Propofol-TIVA versus inhalational anesthesia for cancer surgery

Zara E. Edwards, Leigh J. S. Kelliher

Department of Anaesthesia, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK

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Correspondence to: Dr. Zara E. Edwards. Department of Anaesthesia, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK. Email: zedwards@doctors.org.uk.

Abstract: Cancer represents one of the greatest challenges to healthcare systems globally and the incidence of new cancer cases is increasing year on year. The most common mode of cancer death is not from the primary tumor but as a result of metastatic disease. Loco-regional tumor recurrence depends upon the balance between the metastatic potential of the tumor cells and the integrity of the host's immune response. Surgical resection of the primary tumor is the mainstay of treatment for many cancer types. The concept of surgery-induced metastases is well documented in the literature. One area of particular focus has been in the modifiable perioperative factors that may impact cancer outcomes. This article reviews the existing evidence from in vitro, cohort and controlled trials regarding the impact of propofol-TIVA anesthesia compared with inhalational anesthesia on cancer surgery outcomes. Whilst there are a wealth of animal and human cell line in vitro studies strongly supporting the pro-metastatic effect of inhalational anesthesia and anti-metastatic effect of propofol-TIVA, these models cannot be assumed to have clinical relevance to cancer surgery. The vast majority of existing published human data is single centre and retrospective in design, meaning it is subject to bias and confounders. The evidence that does exist remains mixed with some human studies producing contrary results. More robust, prospectively collected and controlled data is required and there are a number of research studies underway, however conclusive results in this challenging field of research will likely be many years away. Based on the current evidence there can be no clear recommendation for either propofol-TIVA or inhalational anesthesia over the other. However, it seems sensible that whatever anesthetic technique is selected the overall goal should be to minimize perioperative stress and optimize the recovery of the patient.

Keywords: Anesthetics; cancer; inhalational; outcomes; propofol

Introduction

Cancer is the second leading cause of mortality across the world with the global incidence of cancer continuing to rise year on year (1). In 2018 there were greater than 18 million new cancer diagnoses and over 9.5 million deaths. The four commonest cancers are lung, breast, colorectal and prostate with lung responsible for the highest number of deaths, followed by colorectal, gastric and liver cancer respectively (2). The most common mode of cancer death is not from the primary tumor but rather as a result of metastatic disease (3). The global population is ageing and in addition rates of obesity are approaching epidemic proportions (4). Both these factors are independently associated with an increased risk of developing cancer (5) and in combination mean that cancer is set to remain the single biggest challenge to healthcare systems worldwide.

Surgical resection of the primary tumor is the mainstay of treatment for many cancer types and it has been estimated that nearly 80% of cancer patients require an anesthetic

during the course of their therapy (6). Unfortunately, metastatic recurrence is common, even following complete surgical resection with microscopically negative margins. The perioperative period represents a critical time in cancer treatment and it is postulated that perioperative events may greatly influence oncological outcome. This has led to a growing interest surrounding the interplay between anesthetic agents and cancer cell biology and how this may impact long-term cancer outcomes following surgery—such as cancer recurrence, disease free survival, return to intended oncological treatment, the development of tumor metastases and overall survival. Specifically, the role of regional anesthesia, general anesthesia, analgesic agents and non-pharmacological adjuncts on cancer cell modulation have been investigated. In order to consider the potential role of the perioperative anesthetic technique, we need first to understand the biology of cancer tumor recurrence. Simply put, loco-regional tumor recurrence depends upon the balance between the metastatic potential of the tumor cells and the integrity of the host's immune response. One area of particular focus has been the differential impact of inhalational anesthesia when compared with propofol-based intravenous anesthesia (TIVA) on this balance.

The aim of this article is to review the existing evidence regarding the impact of propofol-TIVA anesthesia compared with inhalational anesthesia for cancer surgery on cancer cell biology and oncological outcomes.

Tumor growth and metastasis

Tumor growth and metastasis is a complex process. It is initiated by a genetic mutation (or series of mutations) within a cell that eventually leads to uncontrolled proliferation of that cell and hence growth of the primary tumor. In order to enlarge and invade surrounding tissues the tumor requires a blood supply. Vascularization of the primary tumor is aided by secretion of angiogenic factors such as vascular endothelial growth factors (VEGF) and prostaglandin E2. As the tumor develops it reaches a stage where individual tumor cells detach from the primary and migrate via blood or lymphatic circulation to distant sites within the host. This intravasation requires production and secretion of proteolytic enzymes such as matrix metalloproteinases (MMP) to degrade the basement membrane. Not all tumor cells will survive in the circulation—many will be detected and eliminated by the host's immune system, but the ones that do survive attach themselves to the endothelial cell lining of blood vessels

and migrate to the secondary tissue/organ. Proliferation of a secondary tumor/metastasis at this distant site can then occur through the same mechanisms described above. A variety of proteins, such as cytokines, interleukins and growth factors, may influence this process in different ways, specific to different tumor types.

A competent immune system is vital for protection against the development and growth of malignant tumors with the cell-mediated immune system thought to be of particular importance. Cells such as natural killer (NK) cells, cytotoxic T cells and T helper (Th) cells recognize and eliminate the majority, if not all, of the circulating primary tumor cells. A number of studies have demonstrated how a reduction in NK cell activity correlates with enhanced development of tumors and metastases (7) and an increased activity of cytotoxic T cells correlates with increased 5-year survival in lung and colorectal cancers (8,9). There are many *in vitro* studies that have looked at the different cells and cytokines that constitute cell-mediated immunity and how their levels may alter dependent on anesthesia technique utilized. These will be discussed later.

In essence, the process of tumor growth and metastasis depends upon the balance between factors favoring tumor cell survival and proliferation and the ability of the host's immune system to detect and destroy malignant cells.

Surgery and cancer cell biology

The concept of surgery-induced metastases is well documented in the literature (10). Multiple mechanisms have been proposed to explain this phenomenon. Firstly, surgical tumor manipulation and excision can disrupt both the solid tumor and its blood supply causing inadvertent dispersal of tumor cells into the circulation (11) and in the case of colorectal cancer, spillage of tumor cells into the peritoneal cavity (12). Secondly, the surgical stress response results in a transient impairment in cell-mediated immunity (13), the magnitude of which is relative to the extent of surgical trauma. NK cell activity has been shown to be decreased post-surgery and more so in mice that underwent laparotomy compared to laparoscopy (13). Post-operatively Th2 cells increase and Th1 cells decrease resulting in a decrease in the Th1/Th2 ratio and consequently suppressed cell-mediated immunity. The immunological response is associated with increased secretion of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α, prostaglandin E2), but also the release of anti-inflammatory cytokines (e.g., TGF-β, IL-10 and IL-1

receptor antagonist). These anti-inflammatory mediators override and induce a general systemic immunosuppression, thereby shifting the balance in favor of tumor growth and metastasis. The final mechanism proposed is that tissue trauma caused during surgery results in the release of potent angiogenic factors (VEGF and prostaglandin E2) coupled with a reduction in the levels of anti-angiogenic factors like angiostatin and endostatin (14). The overall effect is to promote angiogenesis and facilitate both local tumor recurrence and the growth of distant metastases. To summarize, surgery itself results in a pro-tumorigenic molecular environment increasing the likelihood of locoregional cancer recurrence.

Anesthesia and cancer cell biology

There exists a plethora of *in vitro* laboratory studies in a variety of both animal and human cancer cell lines describing the potential mechanisms by which different anesthetic agents may affect tumor growth and the development of metastases.

There is widespread *in vitro* evidence supporting the pro-metastatic effect of inhalational anesthetics and mechanisms by which this may occur. One of the earliest papers studying the impact of different anesthetic agents on tumors found that halothane increased the development of lung metastases when lung cancer cells were implanted into the hind feet of mice (15). Another murine study showed comparable results with more lung metastases observed on autopsy in experimental mice injected with intravenous B16 melanoma cells following exposure to halothane or isoflurane (16). In a rat model of breast cancer metastasis, there was increased lung tumor retention after exposure to one hour of halothane and significantly reduced circulating NK cell activity (7). A further study showed reduced NK activating receptor CD16, IL-10 and IL-1β in post-operative serum of patients undergoing primary breast cancer surgery with sevoflurane anesthesia (17). The breast adenocarcinoma MDA-MB-231 cell line showed reduced programmed cell death (apoptosis) in the serum of patients after exposure to a sevoflurane for breast cancer surgery (18) indicating more tumor cells survived. Dose dependent sevoflurane and isoflurane induced apoptosis of human T cells has been observed *in vitro* (19,20), impairing cell-mediated immunity. Isoflurane decreased the post-operative Th1/Th2 ratio in the serum of patients undergoing craniotomy for removal of tumor (21). An *in vitro* study of cultured ovarian cancer cells SK-OV3 exposed to isoflurane showed significantly increased levels of insulin-like growth factor (IGF)-1, IGF-1 receptor, VEGF, angiopoetin-1 and significantly increased production of MMP-2 and MMP-9 (22). IGF-1 and IGF-1 receptor have a key role in the cell cycle and stimulate cell proliferation and suppress apoptosis enhancing cell survival. VEGF and angiopoetin-1 are crucial for angiogenesis and have a role in the neovascularization of tumors. MMP-2 and MMP-9 both mediate breakdown of the extracellular matrix and aid invasion and migration of tumor cells. Upregulation of all these increased the malignant potential of the ovarian cancer cells. Isoflurane enhanced hypoxia-inducible factor (HIF)-1α expression and translocation in cultured human prostate adenocarcinoma PC3 cells *in vitro* (23). Similarly, sevoflurane exposure to *in vitro* glioma stem cells stimulated upregulation of VEGF, HIF-1α and HIF-2α in a time and concentration dependent manner (24). HIFs are a family of transcription factors that facilitate the response to hypoxia, resulting in angiogenesis and promoting cell proliferation. Overexpression of HIFs will result in tumor growth and metastasis.

In contrast, there is extensive *in vitro* evidence for the anti-metastatic effect of propofol-TIVA. A rat model of breast cancer metastasis showed no change in lung tumor retention and no reduction in circulating NK cell activity after exposure to propofol (7). Post-operative serum from patients undergoing primary breast cancer surgery with propofol-TIVA and paravertebral analgesia had increased NK cell activity, no change in IL-10 or IL-1β, and increased apoptosis (17). Clinically relevant levels of propofol-TIVA as a target-controlled infusion inhibited the invasiveness of HeLa human cervical carcinoma cells, HT1080 human fibrosarcoma cells, HOS human osteosarcoma cells and RPMI-7951 human melanoma cell lines. Propofol-TIVA infusion at 40 mg/kg/day also significantly decreased the number of pulmonary nodules at 4 weeks after LM 8 murine osteosarcoma cells were inoculated into mice (25). Propofol has been shown to upregulate cytotoxic T lymphocytes and thus anti-tumor immunity in mice injected with murine thymoma tumor cells (26). Propofol-TIVA and paravertebral combination also significantly reduced cell proliferation, but not migration, when the breast MDA-MB-231 cell line was treated *in vitro* with serum from patients who had undergone breast cancer surgery (27). Jaura *et al*. utilized a similar methodology in their MDA-MB-231 cell line study, showing serum exposed to propofol had more apoptosis compared to serum exposed to sevoflurane anesthesia (18). A study of non-small cell

lung cancer patients undergoing lobectomy showed helper T cells were increased in the propofol-TIVA group (27). There was no change in the post-operative Th1/Th2 ratio in patients undergoing craniotomy with propofol-TIVA anesthesia (28). Propofol had no effect on HIF-1α expression and translocation in cultured human prostate adenocarcinoma PC3 cells *in vitro* (23), but interestingly, propofol was capable of inhibiting the isoflurane induced expression of HIF-1α.

To summarize, these animal and human cell line *in vitro* studies strongly support the pro-metastatic effect of inhalational anesthesia and anti-metastatic effect of propofol-TIVA. Inhalational anesthesia promotes cell proliferation, invasion and migration by increasing IGF-1, IGF-1 receptor, VEGF, angiopoetin-1, HIF-1α, HIF-2α and MMP. In addition, it is associated with defective apoptosis and reduced NK cell activity, IL-10, IL-1β, T lymphocyte levels and decreased the Th1/Th2 ratio, thus impairing cell-mediated immunity. By comparison, propofol-TIVA reduces cell proliferation, maintains apoptosis, increases NK cell activity, increases pro-inflammatory cytokines and does not alter HIF-1α levels or tumor cells throughout surgery.

However, these models cannot be assumed to have clinical relevance to cancer surgery. Many utilized anesthetic agents that are no longer used clinically and *in vitro* conditions remove the cellular environment a cancer cell inhabits and eliminate the host's immune system response. However, they do highlight plausible mechanisms by which propofol-TIVA may be advantageous compared to inhalational agents.

Clinical evidence

So how does this *in vitro* laboratory evidence translate into 'real' patients? What is the clinical evidence? To date, the majority of clinical data comes from retrospective cohort studies. Perhaps one of the most notable of these was published in 2016 by a UK-based group (29). They presented a retrospective analysis of data from over 7,000 patients undergoing cancer surgery at a single centre between June 2010 and May 2013. Patients were divided into either an inhalational anesthesia or a propofol-TIVA group. Any patient receiving both was excluded and they found an increased mortality at one year with inhalational compared to propofol-TIVA of almost 50%. This was independent of patients' ASA score, the surgical severity or the presence of metastases at time of surgery. Multivariate

analysis for type of cancer showed that this increased mortality was principally seen in gastrointestinal and urological cancers perhaps indicating that certain tumor types may be more susceptible to anesthetic modality. It should be noted however that tumor stage was not reported, which may have had an impact on prognosis in the context of their primary outcome.

Another retrospective analysis, this time of 2,838 breast and colorectal cancer patients undergoing surgery between 1998 and 2010 in a single centre in Sweden reported a benefit of propofol over sevoflurane anesthesia in terms of 1-year and 5-year overall survival, however the data was subject to a variety of confounding factors and following a multivariate analysis to account for these, the mortality benefit was no longer found to be statistically significant, forcing the authors to conclude that the study was underpowered and difficult to draw any meaningful conclusions from (30).

A retrospective analysis of 2,856 patients who had undergone gastric cancer resection in a single Chinese centre between 2007 and 2012 compared propofol-TIVA and sevoflurane anesthesia with a primary outcome of overall survival (31). Propofol-TIVA was associated with improved survival compared to sevoflurane after both univariate and multivariate analysis for known confounders.

A single-centre study from Korea retrospectively looked at patients who had undergone elective esophageal cancer surgery either with propofol-TIVA (731 patients) or inhalational anesthesia (191 patients). Inhalational was independently associated with a worse overall survival and recurrence free survival compared to propofol after multivariate analysis and propensity scoring (32).

A further single-centre retrospective analysis looked at 325 patients undergoing modified radical mastectomy for breast cancer over a 2-year period in Korea. General anesthesia was maintained with either propofol-TIVA or sevoflurane and the outcomes of recurrence free survival and overall survival were compared. Whilst overall survival was no different between the groups, the propofol group showed a lower rate of cancer recurrence in the 5 years post-surgery (33). Contrary evidence does exist with another single-centre retrospective analysis of Korean breast cancer patients, this time including 3,500 participants, finding no difference in 5-year recurrence free survival or overall survival between propofol-TIVA and inhalational anesthesia (34). A further retrospective analysis of 943 lung cancer patients comparing propofol-TIVA with inhalational anesthesia found no difference in long term oncological outcome or

Table 1 Ongoing clinical research trials (36)

Trial identifier	Cancer type	Study type	Estimated enrollment number	Study arms	Estimated completion date	Primary outcome	Secondary outcomes
NCT02756312	Malignant glioma	Randomized, triple masking	500	Propofol *vs.* sevoflurane	Dec 2018. Recruitment status unknown	Progression free survival rate up to 6 months post op	
NCT02839668	Breast cancer	Randomized single blind	120	Propofol *vs.* sevoflurane	Sept 2019. Completed	Serum concentration of VEGF-A	Survival
NCT02660411	All cancers	Randomized, single blind	1,200	Propofol *vs.* sevoflurane	Dec 2020. Active, not recruiting	3-year survival	3-year recurrence
NCT02786329	Colorectal cancer	Randomized, quadruple masking	450	Propofol *vs.* sevoflurane	Dec 2021. Recruiting	Survival, recurrence	LOS, post op chronic pain
NCT03034096	All cancers	Randomized double blind	2,000	Propofol *vs.* inhalational	Aug 2023. Recruiting	All-cause mortality	Recurrence free survival
NCT03193710	Colorectal cancer	Case control	260	Propofol *vs.* sevoflurane	Oct 2023. Recruiting	5-year cancer free survival	Recurrence rate, metastasis rate
NCT01975064	Breast and colorectal cancer	Randomized, single blind	8,000	Propofol *vs.* sevoflurane	Dec 2023. Recruiting	5-year survival	1-year survival
NCT04316013	Colorectal and non-small cell lung cancer	Randomized, quadruple blinding	5,736	Propofol *vs.* sevoflurane	May 2025. Not yet recruiting	Disease free survival	Overall survival, days alive and at home, return to intended oncological treatment
NCT04259398	Colon cancer	Randomized double blind	792	Propofol *vs.* sevoflurane	Feb 2026. Recruiting	5-year survival	1/3/5-year recurrence free survival, 1/3-year survival

survival between groups (35).

Clearly more robust, prospectively collected and controlled data is required and there are a number of research studies ongoing [see *Table 1* (36)]. At the time of writing, the number of prospective trials published remains low and those that there are involve relatively small numbers of patients.

One such single-centre prospective randomized controlled trial (RCT) included 28 consecutive bladder cancer patients who underwent radical cystectomy between February 2010 and March 2011 (37). Patients were randomly assigned to receive either propofol/remifentanil TIVA or sevoflurane anesthesia. Serum levels of different cytokines were measured and patients were followed up to assess disease free survival interval, metastasis and overall survival. The propofol-TIVA group showed a significant increase in the pro-inflammatory Th1 cytokine IFN-γ

compared to the sevoflurane group. This was used as a marker of the Th1 response, therefore indicating a tumor suppressive effect of propofol-TIVA. Differences in disease-free survival, overall survival and occurrence of metastases between the two groups were not statistically significant.

Another single-centre prospective RCT from China included 80 female patients undergoing breast cancer resection, who were randomized to receive either sevoflurane anesthesia or propofol/remifentanil TIVA (38). The primary outcome was the preoperative to post-operative change in VEGF-C concentration, a subtype of the VEGF protein family that promotes angiogenesis and lymphangiogenesis. The secondary outcomes were changes in TGF-β concentration, pain assessment scores, post-operative analgesia requirement, recurrence free survival and overall survival. VEGF-C concentration significantly increased after surgery in the sevoflurane group compared

to the pre-operative level in agreement with *in vitro* human cell line data (22), but VEGF-C concentration remained almost unchanged in the propofol-TIVA group. There were no significant changes in TGF-β concentration between the two groups, or before and after surgery. The short term recurrence rates of breast cancer were similar between the two groups likely because they were only followed up for 2 years. Overall survival was the same in both groups. The small number of patients and limited follow up time make it difficult to draw conclusions.

The biggest published prospective RCT to date used data collected from 13 centres in eight countries worldwide (Argentina, Austria, China, Germany, Ireland, New Zealand, Singapore and USA) enrolling patients over an 11-year period starting in January 2007 (39). Women less than 85 years old having potentially curative primary breast cancer resections were enrolled and randomized to either propofol-TIVA with paravertebral block (1,043 patients) or sevoflurane anesthesia with opioid analgesia (1,065 patients) with a primary outcome of local or metastatic breast recurrence. Whilst not specifically designed to compare propofol-TIVA with inhalational anesthesia this study showed that combining different anesthetic techniques in the form of regional anesthesia and propofol-TIVA did not improve recurrence rate or cancer free survival compared to sevoflurane anesthesia and opioid analgesia. To further confuse the picture a significant number of patients in the propofol-regional group appeared to receive sevoflurane during their care episode—some for sedation whilst the regional block was sited. These issues clearly make reaching definitive conclusions over the propofol/inhalational question impossible, but the results are interesting nonetheless.

Several meta-analyses and a systematic review have been performed recently which include many of the retrospective cohort and prospective studies mentioned above. One such included 12 studies (10 retrospective, 2 prospective) with more than 21,000 patients and found a lower all-cause mortality and greater recurrence free survival with propofol-TIVA compared to inhalational anesthesia (40). Another meta-analysis including 10 studies (9 retrospective, 1 prospective) concluded the same, with propofol use associated with greater recurrence free survival (6 studies, 7,866 patients) and improved overall survival (8 studies, 18,778 patients) across numerous cancer types (41). A systematic review including 8 studies drew similar conclusions with propofol-TIVA seeming to lead to decreased mortality and reduced post-operative pulmonary complications in cancer patients (42).

As mentioned, the vast majority of existing published data is retrospective in design, meaning it is subject to bias and the confounding effects of variation in factors such as patient demographics/comorbidities, surgical and anesthetic practices, adjuvant therapies received and stage of cancer at time of surgery. What can be concluded is that these large retrospective cohorts have identified a trend (backed by evidence from laboratory studies) that propofol-TIVA may confer improved recurrence free survival and overall survival when compared to inhalational anesthesia and this warrants further research. The challenges are many; in addition to those mentioned above, there is the timescale that such studies would need to be conducted over in order to reach meaningful outcomes and the possibility that new treatments/therapies will emerge altering the landscape and rendering findings obsolete before they can be completed. Nevertheless, with cancer and the need for cancer surgery and anesthesia so prevalent and only set to increase it is vital that answers to these important questions are sought.

Future research

There are a number of large prospective clinical trials underway which are directly investigating the difference between propofol-TIVA versus sevoflurane in terms of cancer recurrence and survival in a variety of different cancer types (*Table 1*). Whilst it will take years for the results of some of these ongoing trials to emerge, hopefully they will ultimately provide clarity over this issue.

Conclusions

'Cancer' is an umbrella term encompassing a huge variety of conditions arising from different cell types/tissues with different phenotypic and genetic characteristics. Patients suffering from cancer present at different stages of disease, with different risk factors including variations in age, sex, comorbidities, exposure to environmental factors, genetic traits. In addition to this, the existing treatments vary widely according to availability, healthcare systems, current evidence, local practices and personal choice. Despite all of this, two broad themes remain; firstly, the central disease process involves uncontrolled proliferation of cells leading to the disruption of the anatomy and function of normal tissues and secondly, surgery and anesthesia form at least part of the treatment of the majority of cancers. The idea that events that take place during the perioperative

period may influence cancer outcome and survival is not a new one, however as the understanding of how cancer grows and develops and what factors influence this at a cellular level has increased, so has the appreciation of how specific anesthetic agents/interventions may impact this process. In this article we have looked specifically at the current evidence surrounding the hypothesis that the use of inhalational anesthesia or propofol-TIVA may produce differing effects on locoregional tumor recurrence following surgery. Whilst there is a wealth of *in vitro* evidence demonstrating mechanisms via which this effect may be promoted, thereby giving biological plausibility to this theory, the picture remains mixed with some studies producing contrary results. The clinical evidence base remains relatively weak with the vast majority of existing studies being single-centre retrospective cohort studies and consequently vulnerable to multiple sources of bias. Large prospective RCTs are needed and are now underway, however conclusive results in this challenging field of research will likely be many years away. In the meantime, clinicians must continue to make the best decisions possible taking into account all of the circumstances surrounding the individuals they are treating. Based on the current evidence there can be no clear recommendation for either propofol-TIVA or inhalational anesthesia over the other. However, it seems sensible that whatever anesthetic technique is selected the overall goal should be to minimize perioperative stress and optimize the recovery of the patient allowing rapid return to normal function. It is perhaps interesting to note that whilst no clinical evidence exists to definitively recommend propofol-TIVA over inhalational anesthesia for the purpose of improving oncological outcomes, there are no current studies demonstrating it is worse.

Acknowledgments

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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