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REVIEW

Anesthesia Options and the Recurrence of Cancer: What We Know so Far?

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Abstract: Surgery is a critical period in the survival of patients with cancer. While resective surgery of primary tumors has shown to prolong the life of these patients, it can also promote mechanisms associated with metastatic progression. During surgery, patients require general and sometimes local anesthetics that also modulate mechanisms that can favor or reduce metastasis. In this narrative review, we summarized the evidence about the impact of local, regional and general anesthesia on metastatic mechanisms and the survival of patients. The available evidence suggests that cancer recurrence is not significantly impacted by neither regional anesthesia nor volatile or total intravenous anesthesia.

Keywords: neoplasm, surgery, anesthesia, recurrence

Introduction

Cancer is a major cause of mortality worldwide with an estimated 9.6 million deaths per year.[1] Lung, colorectal, stomach and liver are the most common types of cancer and account for nearly half of cancer-related deaths. By 2040, it is estimated that there will be approximately 30 million new cases of cancer.[1] It is projected that a large proportion of patients will need surgery for tumor resection despite rapid and substantial advances in treatments, including chemotherapy, targeted therapy, radiotherapy, and immunotherapy.

Surgery causes the local and systemic release of inflammatory mediators and promotes high levels of angiogenesis. Also, surgery is associated with high concentrations of circulating catecholamines and immunosuppression that can last for days or weeks postoperatively, making this a period of high vulnerability for complications and tumor progression.[2,3] Some evidence suggests that certain anesthetics or anesthesia techniques may also affect the growth of the so-called minimal residual disease.[4,5] Total intravenous anesthesia (TIVA) with propofol was associated with prolonged overall survival in patients with metastatic and non-metastatic cancers.[6] Local anesthetics and regional anesthesia can also modify cancer progression by limiting inflammation, immunosuppression, and angiogenesis.[4,7,8] However, a recently published randomized controlled trial concluded that compared to sevoflurane-based general anesthesia, regional anesthesia did not improve the survival nor reduced recurrences after breast cancer surgery.[9]

Investigators have hypothesized that the technique of general anesthesia (total intravenous vs volatile-based or regional anesthesia) has a significant impact on caner progression. In this narrative review, we will discuss the evidence of the impact of different anesthetics and anesthesia techniques on metastatic progression

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after surgery. Our work will include current basic, translational and clinical studies addressing the effects and association between different anesthetics and cancer progression.

Perioperative Metastasis Formation

The growth of metastatic colonies outside the primary tumor is a multi-step process. Colonization of distant sites by circulating tumor cells (CTCs) is a rate-limiting step during the metastatic process. In general, it is well accepted that metastasis may be part of a dominant clonal subpopulation that originated within the primary tumor.[10] By virtue of tumor-secreted factors and tumor-secreted exosomes, the microenvironment of distant organ sites is modified into prometastatic niches that contain recruited stem cells and stromal cells.[11]

A critical event in the metastasis process is the epithelial-mesenchymal transition (EMT) that CTCs undergo to increase mobility and invasiveness (Figure 1). The EMT process is orchestrated by transcription factors (ie, Snail, Slug, Twist, and Zeb1) that, in turn, respond to extracellular molecular signals occurring in the nearby tumor stroma such as inflammation.[12] Once in the bloodstream, CTCs interact with other cells, including platelets and lymphocytes. Platelets can provide shelter to CTCs and hide them from lymphocytes such as natural killer (NK) cells. Also, activated platelets can release soluble mediators such as transforming-growth factor beta (TGF-β), platelet-derived growth factor (PDGF), and adenosine triphosphate (ATP). These factors are known to suppress the killing activity of NK cells and enhance vascular permeability.[12] Once CTCs extravasate via transendothelial migration (TEM), they find the extracellular tissue stroma where they may reside and proliferate. Some of those cells in the new forming metastatic colony retain features of cancer stem cells (CSC), which have tumor-initiating ability and can drive colony expansion.[12]

It is speculated that micrometastasis or dormant colonies are contained by immune surveillance or by the lack of supporting factors that can sustain cell proliferation.[13] Thus, the transition from single cell or colony of cells to micrometastasis to clinically relevant metastasis can take months to years.[12,14] Remarkably, surgery can facilitate the homing of CTCs and growth of micrometastasis by releasing cytokines, angiogenic factors, and catecholamines. In mice, surgery-induced inflammation promoted

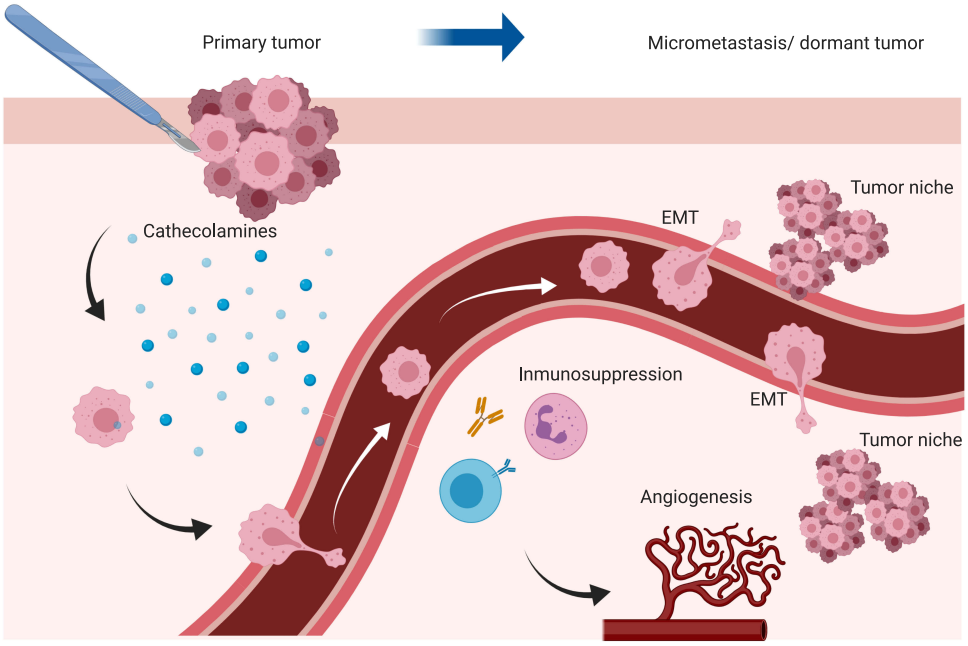

Figure 1 Perioperative events that influence tumor metastasis and cancer recurrence. Surgery for tumor resection triggers the release of catecholamines, immunosuppression, and angiogenesis. It has been speculated that these factors facilitate epithelial-mesenchymal transition (EMT) and promote a conducive microenvironment (tumor niche) for cells to migrate, invade and proliferate.

the outgrowth of T cell restricted distant tumors by mobilizing myeloid cells and recruiting tumor-associated macrophages.[15]

Neutrophil extracellular traps (NETs) has been recognized as a mechanism that facilitates colonies formation. NETs are web-like structures formed by DNA fragments and proteins that can sequester CTCs.[16,17] In mice, surgery promoted NETs and micrometastasis. When mice were treated daily with DNAase after surgery, it reduced tumor growth.[16] Circulating neutrophils entrapped in clumps formed by platelets or in the extracellular matrix can also provide a conducive environment for CTCs to survive by further suppressing the activity of NK cells.[12]

Several studies have shown a decrease in the number and function of circulating NK cells after surgery.[3] Subsequently, investigations revealed that surgery-induced reduction in circulating NK killing activity could promote metastasis (Figure 1).[18] Interestingly, it has been demonstrated that the transcriptome profile of circulating NK cells is significantly different from NK cells located in metastasis suggesting that the role of NK cells in the micrometastatic niche during surgery might be different from those circulating.[19]

It is worth considering that the metastatic process is also affected by factors including the use, timing, and completion of adjuvant therapies (ie, chemotherapy, radiation, and immunotherapies). For instance, it is now well understood that for some malignancies, delaying the return to oncological therapies after surgery has a significant impact on patients' survival.[20] Another important factor associated with cancer progression is the occurrence of complications in the postoperative period and perioperative blood transfusions.[21,22] Therefore, it has been suggested that patients undergoing cancer surgery should be evaluated and treated by a multidisciplinary team dedicated to assess modifiable risks and propose a coordinated plan of measures (ie, anemia treatment) tailored to reduce postoperative complications and accelerate recovery.[23]

In the following sections, we will discuss how anesthetics may or may not interfere with the process involved in the metastatic process and metastatic cancer progression.

Local Anesthetics

Local anesthetics can act on several steps of the metastatic process (Figure 2). The administration of intravenous lidocaine (1.5 mg/kg followed by infusion of 2 mg/kg) under sevoflurane anesthesia reduced postoperative lung metastasis by decreasing serum concentrations of the metalloproteinase (MMP)-2 in a murine surgical breast cancer model.[24,25] It was speculated that changes in MMP-2 resulted in a reduced ability of CTCs to form metastasis.[24] Local anesthetics also impair the movement of malignant cells in vitro.[26,27] As an example, ropivacaine inhibited migration and invasion of esophageal and colorectal cancer cells.[26] Although, the anti-metastatic effects of ropivacaine in esophageal cancer cells were independent of voltage-gated sodium channel (VGSCs) blockade and mediated by inhibition of RhoA, Rac1 and Ras, they were dependent on Nav1.5 blockade in colorectal cancer cells.[26,28]

VGSCs regulate the metastatic activity of cancer cells. These channels are located in the cell membrane, in particular in cellular structures called invadopodia, which are essential for degrading the extracellular matrix.[29] In the invadopodia, VSGCs promote polymerization of actin filaments via Src signaling.[29] In vitro studies demonstrate that downregulation of VSGCs via shRNA inhibits tumor invasion by blocking the invadopodia.[30]

Local anesthetics have shown anti-angiogenic effects. Lidocaine (30 mg/kg) inhibited tumor growth in mice bearing melanoma tumors by inducing apoptosis in endothelial cells.[31] In these cells, lidocaine suppressed VEGF-increased phosphorylation of VEGF receptor 2.[31] Similarly ropivacaine induced apoptosis on tumor-associated endothelial cells by inducing mitochondrial dysfunction.[32] Local anesthetics also modulate inflammation (Figure 3). Notably, lidocaine reduced pro-inflammatory cytokines [ie, tumor necrosis factor (TNFα) and interleukin-6 (IL-)] in a mice model having breast cancer surgery.[33] Furthermore, lidocaine and ropivacaine inhibited migration and invasion of lung cancer cells by inhibiting TNFα- induced phosphorylation of Src and reducing the expression of ICAM-1 (glycoprotein essential for cellular adhesion).[34,35] A reduction in the concentrations of pro-inflammatory concentrations is observed in humans receiving intravenous lidocaine during surgery.[36]

Increased vascular permeability, as it occurs during periods of exaggerated inflammation, facilitates TEM and can promote the implant of metastatic cells. The intravenous administration of lidocaine (1 and 3 mg/kg) to mice inoculated with LPS significantly reduced lung permeability. The postulated mechanisms included a reduction of inflammatory cytokines (TNFα, IL-6, and MCP-1) and impairment of antigen presentation, a process done by dendritic cells (DC) (Figure 3).[37,38] As an example,

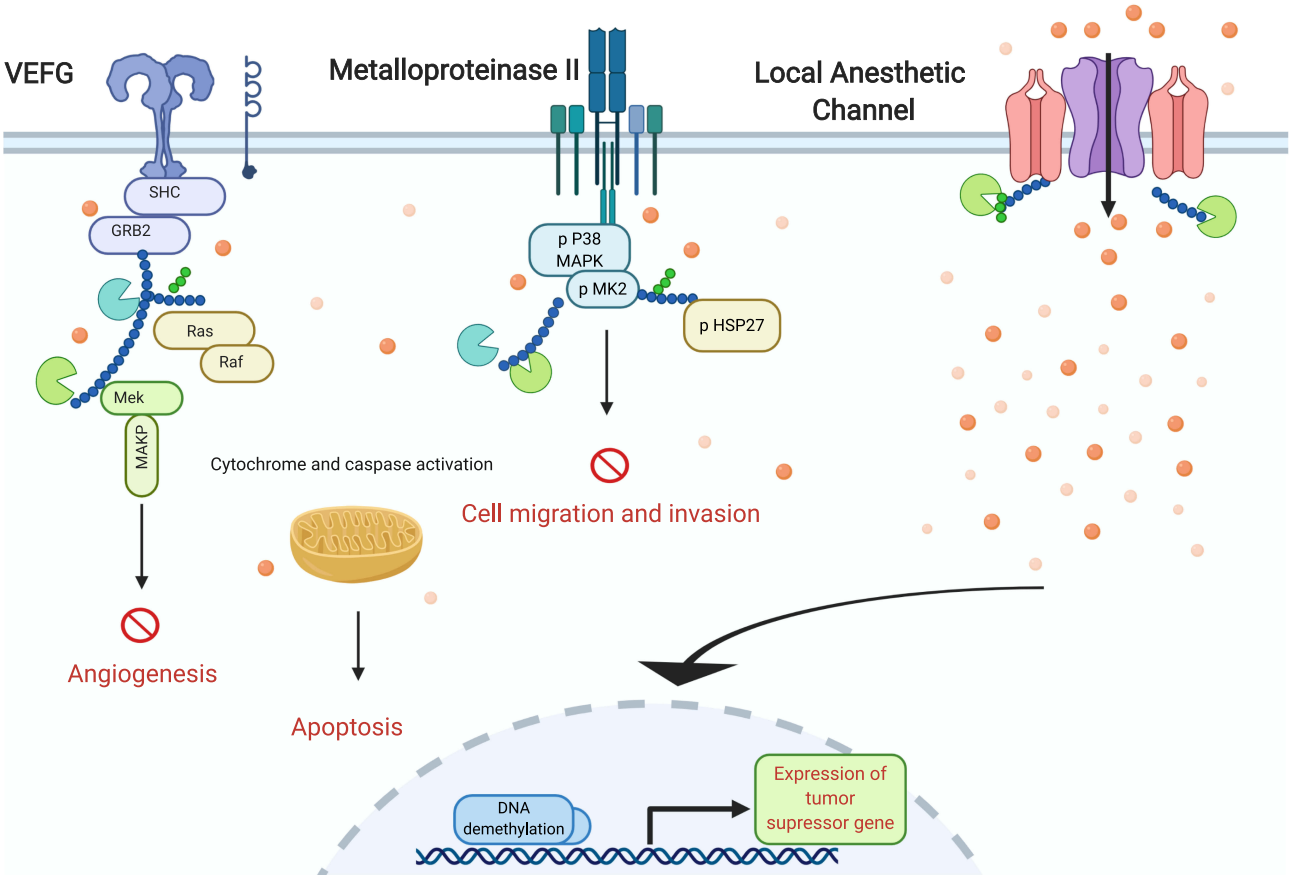

Figure 2 Several mechanisms have been associated with the anti-metastatic effects of local anesthetics. Intracellular they inhibit signaling events linked to angiogenesis, migration, and invasion.
Abbreviation: VEGF, vascular endothelial growth factor.

lidocaine inhibited the expression of proinflammatory cytokines in bone marrow-derived DC that were stimulated with LPS.[38]

Inflammation also induces DNA methylation, a mechanism linked with metastasis.[39,40] Local anesthetics such as lidocaine and ropivacaine induce, in vitro, DNA demethylation in breast cancer cells which correlates with the overexpression of the tumor suppressor genes (*RARB2* and *RASSF-1A*).[41–43] Lidocaine also induces modulation of microRNAs.[44–47] Treatment of lung cancer cells with 8 mM of lidocaine significantly increased the expression of miR-539, which then induced the downregulation of the epidermal growth factor receptor (EGFR) and suppressed migration and invasion.[45] The intravenous injection of lidocaine (1.5 mg/kg) to mice bearing retinoblastoma caused significant tumor reduction by inducing the expression of miR520a-3p and inhibiting EGFR.[46] MicroRNAs are also involved in chemo-resistance. Lidocaine, in vitro, inhibited the expression of miR-21 and sensitized chemo-resistant lung cancer cells to cisplatin.[48] On the other hand, lidocaine by inducing the expression of miR-493 down-regulated the transcription factor Sox-4, which ultimately sensitized melanoma cells to the effect of 5-fluorouracil.[49]

Another described mechanism that can contribute to the anti-metastatic effects of local anesthetics include the induction of oxidative stress, and a reduced formation of MMP-9.[30,34,35,50,51] Local anesthetics act on different components of the innate and adaptive immune system has been investigated experimentally and in humans. We demonstrated that lidocaine in clinically relevant concentrations increased the in vitro cytotoxic activity of NK cells by stimulating the release of perforins (Figure 3).[52,53] In humans with abdominal pain, an intravenous injection of 1 mg/kg of lidocaine preserves the count and function of circulating NK cells.[54] Few studies have investigated the impact of intravenous lidocaine on lymphocytes counts or function during and after oncologic surgery.[54,55] Wang et al conducted a randomized

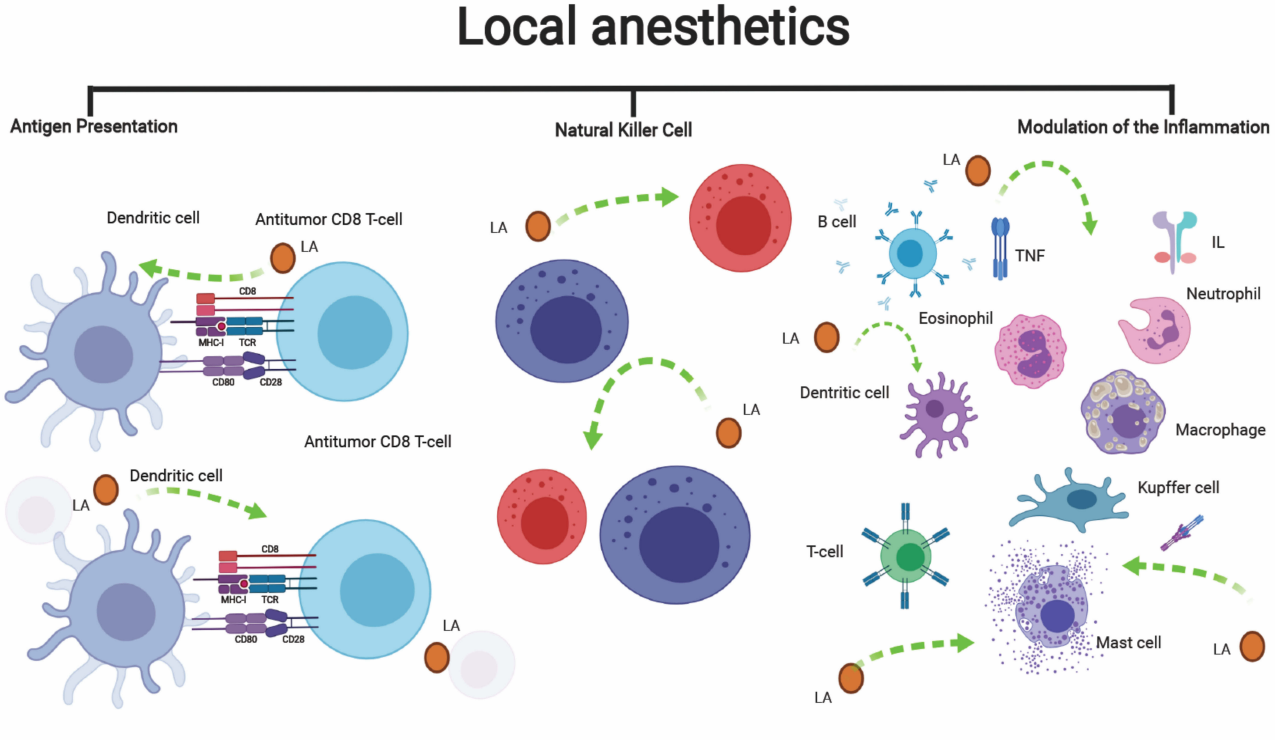

Figure 3 Effect of local anesthetics on immune and inflammatory cells. Local anesthetics modulate the activity of different immune cells. They potentiate natural killer cells cytotoxicity, facilitate antigen presentation, and have shown to modulate the function of neutrophils, macrophages, and dendritic cells.
Abbreviations: LA, local anesthetics; TNF, tumor necrosis factor.

controlled trial (RCT) in women having a radical hysterectomy and compared the effects of lidocaine versus placebo on peripheral blood lymphocytes. The postoperative proliferative rate of lymphocytes was higher in patients treated with lidocaine.[55] The authors speculated that lidocaine protected lymphocytes by preserving the IFN-g/IL-4 ratio and by decreasing inflammation, as demonstrated by lower circulating concentrations of the high mobility group box-1 protein.[55] Similarly, patients with abdominal pain had a preserved CD4/CD8 ratio, and normal T and B cell counts after injection of 1.5 mg/kg of lidocaine.[54]

Local (Infiltration or Intravenous) vs General Anesthesia: Human Studies

To date, there is no strong evidence from human studies indicating that local anesthesia modifies oncologic outcomes after cancer surgery (Table 1). Schalengenhauff et al included 4329 patients with melanoma and showed that the use of general anesthesia was associated with a decreased survival rate.[56] A more recent retrospective study suggests that tumescent local anesthesia, in comparison to general anesthesia, is associated with longer metastasis-free survival also after melanoma surgery. However, overall and disease-free survival were not affected.[57]

Zhang et al recently assessed the impact of intravenous lidocaine on cancer progression. The authors reported that the intraoperative use of lidocaine was associated with longer overall survival in patients undergoing pancreatic cancer surgery.[58] Several randomized controlled trials are being conducted in patients with breast (NCT01204242; NCT01916317), pancreatic (NCT0408278), lung (NCT04074460) and colorectal (NCT04074460) cancers.

Regional vs Opioid-Based Analgesia: Humans Studies

Since 2008 there has been an increase in human studies testing the impact of regional anesthesia on cancer recurrence or recurrence-free survival after surgery.[9,56,59-89] The findings are controversial.[8,59,90] However, a recent RCT could not confirm the anti-cancer effects of regional anesthesia in women undergoing breast cancer surgery.[9] Patients were randomized to either regional anesthesia (preferentially paravertebral block) with propofol sedation

Table 1 Summary of Clinical Studies, Systematic Reviews and Meta-Analysis on the Impact of Regional Anesthesia/Analgesia in Cancer Outcomes

Type of Cancer	Author (Year)	Type of Study	Intervention	Overall Survival	Recurrence-Free Survival
Breast	Sessler et al (2019)[9]	RCT	PVB-GA vs GA	No difference	No difference
Breast	Perez-Gonzalez (2017)[59]	SR (6 studies)	PVB-GA vs GA	No difference	1 study showed benefit of PVB-GA, 1 study showed negative impact of PVB-GA, 4 studies showed no difference
Multiple (Breast, prostate, gastroesophageal, and colorectal)	Ma (2014)[90]	MA (10 studies)	EA-GA vs GA	Not studied	No difference overall. No difference for colorectal alone. For prostate cancer, an increased survival with EA-GA was found.
Colorectal	Cummings (2012)[61]	Retrospective	EA-GA vs GA	No difference	Increased with GA-EA
Colorectal	Gottschalk (2010)[62]	Retrospective	EA-GA vs GA	Not studied	No difference
Colorectal	Gupta (2011)[63]	Retrospective	EA-GA vs Spinal vs GA	Increased for rectal cancer, no difference for colon cancer	Not studied
Colorectal	Day (2012)[64]	Retrospective	EA-GA vs Spinal vs GA	No difference	No difference
Colorectal	Kim (2016)[65]	RCT	LA wound infiltration vs IVPCA	Not studied	No difference
Colorectal liver metastasis	Zimmitti (2016)[66]	Retrospective	EA-GA vs GA	No difference	Increased with EA-GA
Colorectal liver metastasis	Gao (2019)[67]	Retrospective	EA-GA vs GA	Not studied	Increased with GA
Gastroesophageal	Perez-Gonzalez (2018)[69]	SR (6 studies)	EA-GA vs GA	3 studies showed benefit of EA-GA	1 study showed benefit of EA-GA
Glioblastoma	Zheng (2017)[70]	Retrospective	Scalp block vs No block	Not studied	Increased with scalp block
Glioblastoma	Cata (2018)[71]	Retrospective	Scalp block vs No block	No difference	No difference
Hepatocellular	Lai (2012)[72]	Retrospective	EA vs GA	Not studied	Increased with GA
Multiple (Intra-abdominal, Prostate and Colorectal)	Cakmakkaya (2014)[89]	MA (4 RCTs subanalysis studies)	EA-GA vs GA	No difference	No difference
Laryngeal and Hypopharyngeal	Merquiol (2013)[73]	Retrospective	EA-GA vs GA	Increased with EA	Increased with EA

(*Continued*)

Table 1 (Continued).

Type of Cancer	Author (Year)	Type of Study	Intervention	Overall Survival	Recurrence-Free Survival
Lung	Cata (2013)[74]	Retrospective	EA vs PCA vs EA-IVPCA	No difference	No difference
Lung	Lee (2017)[75]	Retrospective	EA vs PVB vs IVPCA	Increased with PVB than any other technique. EA and PCA were not different.	No difference
Melanoma	Schlagenhauff (2000)[56]	Retrospective	LA vs GA	Decreased with GA	Not studied
Melanoma	Gottschalk (2012)[78]	Retrospective	Spinal vs GA	No difference	Not studied
Ovarian	De Oliveira (2011)[79]	Retrospective	EA (intra and postop)-GA vs Postop-only EA vs IVPCA	Not studied	Increased with EA-GA
Ovarian	Lin (2011)[80]	Retrospective	EA vs GA-IVPCA	Increased with EA	Not studied
Ovarian	Capmas (2012)[81]	Retrospective	EA vs No EA	No difference	No difference
Ovarian	Lacassie (2013)[82]	Retrospective	EA vs No EA	No difference	No difference
Ovarian	Tseng (2018)[83]	Retrospective	EA vs IV-PCA	Increased with EA	Increased with EA
Ovarian	Zhong (2019)[84]	Retrospective	EA vs GA-IVPCA	No difference	Not studied
Ovarian	Elias (2015)[85]	Retrospective	EA-GA vs GA	Not studied	No difference
Multiple (Ovarian, Gastrointestinal, Prostate, Breast)	Grandhi (2017)[86]	MA (28 observational studies)	RA vs GA	No difference	No difference
Prostate	Lee (2015)[87]	MA (10 retrospective studies)	EA vs Opioid-based analgesia	Increased with EA	No difference

Abbreviations: EA, epidural anesthesia/analgesia; IV-PCA, intravenous patient-controlled analgesia; GA, general anesthesia; RA, regional anesthesia/analgesia; RCT, randomized-controlled trial; LA, local anesthetic; PVB, paravertebral block; MA, meta-analysis; SR, systematic review.

or sevoflurane/opioid-based general anesthesia.[9] It can be speculated that regional anesthesia probably did not produce a robust immunomodulatory or anti-inflammatory effect and/or, the concentrations of local anesthetics in micrometastatic niches may not have been high enough to produce significant effects.[91–93] In line with this notion, Kim et al concluded that continuous local wound infiltration did not impact one-year recurrence rate after colorectal cancer surgery despite a statistically significant improvement in NK cell function postoperatively.[65] Another factor was the short-term exposure to the intervention. Perioperative immune suppression and inflammation can last beyond the "protective" effects of regional anesthesia. Our group demonstrated in patients having major oncologic surgery, the serum IL-6 levels do not return to preoperative concentrations even two weeks after surgery.[94] Furthermore, the immune "protective" effects attributed to regional anesthesia in sub-studies of

Sessler's trial indicate that such benefits were not clinically relevant.[95,96] Other studies have been designed to test whether regional anesthesia can improve survival or reduce recurrence after bladder (NCT:03597087), non-small cell lung cancer (NCT02840227), colorectal (NCT02786329), and pancreas (NCT03245346).

In summary, the available evidence indicates that the impact of regional anesthesia on cancer recurrence might be negligible or not existent. It remains unknown whether perioperative intravenous lidocaine infusion has any impact on cancer progression.

General Anesthetics and Cancer Progression

Volatile Anesthetics

General anesthetics modify intracellular signaling mechanisms involved in metastasis. Isoflurane (1%-2%) increases migration and invasion of lung cancer cells by promoting Akt/mTOR activation and by promoting the release of MMPs.[97] In ovarian cancer cells, two-hour exposure to isoflurane (1.7 MAC), sevoflurane (1.7 MAC), or desflurane (1.7 MAC) stimulated the mRNA expression of VEGF-A, CXCR2, TGF-β and MMP-11, which correlated with increased cell migration.[98] Also, in ovarian cancer cells, isoflurane (2%) increased the release of VEGF, angiopoietin-1 and MMP-2, and 9.[99] Sevoflurane (3.6%) stimulated the metastatic potential of renal cancer cells and induced their chemo-resistance to cisplatin. These pro-metastatic effects were linked to an increase in the expression of TGF-B1, TGF-BRII and downregulation of Smad3.[100] In a melanoma mice model, isoflurane (1.3 MAC) anesthesia promoted pulmonary metastasis.[101]

As mentioned previously, platelets may play a critical role in CTCs' ability to survive in the bloodstream and attached the endothelium. Lung cancer cells co-cultured with platelets obtained from patients anesthetized with sevoflurane or isoflurane showed increased invasive properties compared to cancer cells incubated with control platelets.[102] Similarly, the culture of colorectal or breast cancer cells with serum obtained from patients receiving sevoflurane anesthesia promoted cell survival in comparison to the serum from propofol-treated patients.[103,104]

Volatile anesthetics can also impair the immune surveillance system. In animals, volatile anesthetics inhibit the function of NK cells, which correlates with an increased metastatic burden.[105] A reduction in the expression of the adhesion molecule leukocyte-associated antigen-1 and decrease in cell-to-cell contact with their target cancer cells has been implicated in the suppressive effects of isoflurane and sevoflurane on NK cells' activity.-[106] Interestingly, Meier et al suggested that the impact of volatile anesthetics such as isoflurane on the immune system are sex-depended.[107] For instance, when male mice were treated with isoflurane, the author observed not only faster tumor growth compared to controls but also faster tumor growth compared to female counterparts.[107] The investigators demonstrated that an immune-mediated mechanism was implicated in their findings since melanoma growth was absent in mice lacking functional T and B cells.[107]

In vitro and animal studies have also demonstrated that general anesthetics may have anti-metastatic effects.[108,109] High concentrations (5% and 10%) of sevoflurane inhibited migration and invasion of osteosarcoma cells, which was associated with the inhibition of EMT markers, including fibronectin and N-cadherin.[108] Similarly, sevoflurane (4.1%) inhibited glioma cell migration by inducing the expression of miR-124-3p and suppressing ROCK signaling.[109] Colorectal cancer cells also exposed to 1% of sevoflurane showed impaired migration and invasion; an effect that was mediated by inhibition of both, miR-203 expression and ERK signaling.[110] Under in vitro hypoxic conditions, sevoflurane (3.5%) suppressed the ability of lung cancer cells to migrate and invade the extracellular matrix by inhibiting the expression of (hypoxia-inducible factor) HIF-1α, which resulted in low levels of XIAP and survivin.[111] However, Gallyas et al could not demonstrate that isoflurane influenced the expression of HIF-1α in renal cancer cells.[112]

Propofol

Propofol is the most common hypnotic used for TIVA. Most in vitro and in vivo animal studies indicate that propofol has significant anti-metastatic effects.[113,114] One of the proposed mechanisms is the downregulation of the STAT3/HOTAIR signaling pathway, which suppresses transcription factors Slug and HIF-1α and induces silencing of the NET1 gene; all changes associated with decreased migration and invasion in cancer cells. A second mechanism involves the upregulation of miR-124-3p.1, miR-135b, miR-361, miR-410-3p, miR-328, and lncRNA DGCR5. A consequence of those epigenetic changes is in vitro inhibition of EMT, which correlates with low levels of N-cadherin and MMPs.[113]

Table 2 Summary of Clinical Studies Comparing TIVA vs Inhalational Anesthesia with Respect to Cancer Outcomes

Type of Cancer	Author (Year)	Type of Study	Intervention	Overall Survival	Recurrence-Free Survival
Appendiceal (HIPEC)	Cata (2019)[128]	Retrospective	TIVA (Opioid-sparing) vs Inhalational-Opioid	No difference	No difference
Breast	Sessler (2019)[9]	RCT subanalysis	TIVA vs Inhalational	No difference	No difference
Breast	Lee (2016)[129]	Retrospective	TIVA vs Inhalational	No difference	Increased with TIVA
Breast	Yoo (2019)[130]	Retrospective	TIVA vs Inhalational	No difference	No difference
Breast	Yan (2018)[125]	RCT (Not powered for OS or RFS)	TIVA vs Inhalational	No difference	No difference
Cholangiocarcinoma	Lai (2019)[131]	Retrospective	TIVA vs Inhalational	Increased with TIVA	TIVA group showed a decreased rate of metastasis.
Colorectal	Wu (2018)[132]	Retrospective	TIVA vs Inhalational (Desflurane-specific)	Increased with TIVA	Not studied
Esophageal	Jun (2017)[133]	Retrospective	TIVA vs Inhalational	Increased with TIVA	Increased with TIVA
Gastric	Zheng (2018)[134]	Retrospective	TIVA vs Inhalational	Increased with TIVA	Not studied
Gastric	Oh (2019)[135]	Retrospective	TIVA vs Inhalational	No difference	No difference
Glioblastoma	Cata (2017)[136]	Retrospective	Isoflurane ± Propofol vs Desflurane ± Propofol	No difference	No difference
Hepatocellular	Lai (2019)[137]	Retrospective	TIVA vs Inhalational (Desflurane-specific)	Increased with TIVA	Increased with TIVA
Lung	Oh (2018)[138]	Retrospective	TIVA vs Inhalational	No difference	No difference
Lung	Xu (2017)[139]	RCT (Not powered for OS or RFS)	TIVA vs Epidural/ Inhalational	No difference	No difference
Multiple (Breast, Esophageal, Lung)	Yap (2019)[140]	MA (10 studies)	TIVA vs Inhalational	Increased with TIVA	Pooled data from 6 studies showed increased with TIVA

(*Continued*)

Table 2 (Continued).

Type of Cancer	Author (Year)	Type of Study	Intervention	Overall Survival	Recurrence-Free Survival
Multiple (Breast, Gastrointestinal, Gynecological, Sarcoma, Urologic, Other)	Wigmore (2016)[6]	Retrospective	TIVA vs Inhalational	Increased with TIVA	Not studied
Multiple (Breast, Gastrointestinal, Liver, Lung)	Hong (2019)[141]	Retrospective	TIVA vs Inhalational	No difference	Not studied
Multiple (Breast, Gastrointestinal, Urologic, Glioma, Lung)	Jin (2019)[142]	MA (12 studies)	TIVA vs Inhalational	Pooled effects favor TIVA, not individualized by cancer type.	Pooled data from 5 studies on recurrence showed no significant difference. TIVA is favored in breast cancer. Pooled data specifically on RFS on 3 studies favor TIVA.
Ovarian	Elias (2015)[85]	Retrospective	Inhaled Anesthesia (Sevoflurane/ Desflurane) vs TIVA	Not studied	Increased with desflurane

Abbreviations: RCT, randomized controlled trial; HIPEC, hyperthermic intraperitoneal chemotherapy; TIVA, total intravenous anesthesia; OS, overall survival; RFS, recurrence-free survival; MA, meta-analysis.

Adhesion molecules located on the surface of endothelial cells are needed to initiate TEM. HUVEC cells treated with different concentrations (5, 25, and 50 μM) of propofol showed low levels of the adhesion molecules E-selectin, VCAM-1, and ICAM-1. These changes in the expression of the adhesion molecules correlated with a reduction in the expression of HIF-1α, and inhibition of Akt and CaMKII phosphorylation.[114] Propofol also has anti-angiogenesis effects as demonstrated in experiments in which it suppressed the invasion of endothelial cells and vessel formation.[115]

The proposed mechanisms behind the anti-angiogenic effects of propofol include the downregulation of S100A4 in endothelial cells and inhibition of the release of VEGF from cancer cells.[115,116] Sen et al conducted an RCT to investigate the effect of propofol in combination with regional analgesia (in comparison to sevoflurane anesthesia) on serum concentrations of VEGF in patients having lung cancer surgery.[117] Patients receiving sevoflurane had significantly higher concentrations of VEGF.[117] Lastly, a proteomic analysis from head and neck cancers demonstrated that the tumors from patients who received sevoflurane anesthesia had higher expression HIF-2α and phosphorylated p38 MAPK in comparison to those receiving propofol.[118]

Propofol can protect against immunosuppression by promoting cytotoxicity activity of NK cells, decreasing pro-inflammatory cytokines and inhibiting prostaglandin E2 (PGE2) and cyclooxygenase (COX) activity. In vitro, propofol stimulated the function and triggered the proliferation of NK cells obtained from healthy subjects and patients with cancer. Such effect on NK cells has been linked to an increase in the expression of granzyme B, IFNγ, and activating surface receptors (CD16, NKp30, NKp44, and NKG2D) as well as a reduction in the formation of PGE2.[119–121] The beneficial effect of propofol in tumor metastasis has been demonstrated in animals. When rats having surgery were anesthetized with propofol the function of NK cells remained unchanged and metastatic formation was lower than animals receiving volatile anesthetics.[105]

In women undergoing breast or cervical cancer surgery, the use of propofol for TIVA in combination with regional anesthesia increased the number of NK and T helper cells in the primary tumor tissue and it was associated with significantly less lymphopenia.[96] Similar findings were

observed in circulating lymphocytes of surgical patients with tongue cancer who received TIVA in comparison to sevoflurane.[122,123] In contrast two independent groups of investigators, did not observe any significant changes cytokines (IL-6, IL-10, and IL-12 TGF- β) and in regulatory T cell cluster differentiation in women randomized to have breast cancer surgery under TIVA or sevoflurane general anesthesia.[124,125] Similarly, inflammatory and immune scores were not different between patients who received general volatile versus TIVA for pancreatic cancer surgery or during cytoreduction with hyperthermic intraperitoneal chemotherapy.[126,127]

TIVA vs Volatile Anesthesia: Human Studies

Because of the anti-metastatic effects of TIVA in experimental conditions, there has been a growing interest in translating such beneficial effects into human studies.[6,9,85,125,128-142] The most extensive study was conducted by Wigmore et al, who retrospectively reviewed the impact of propofol-based general anesthesia vs volatile anesthesia in more than 7000 patients.[6] The authors reported a significant benefit in overall survival (HR 95% CI: 1.59, 1.30–1.95) in patients receiving propofol, even after adjusting for metastatic disease.[6] Several much smaller retrospective studies have demonstrated similar results (Table 2). In 2019, a meta-analysis of 10 retrospective studies concluded that the use of TIVA during cancer surgery is associated with significant improvements in recurrence-free and overall survival.[140] However, TIVA was associated with the most significant impact on the survival of patients with gastrointestinal malignancies.[140] Since the meta-analysis publication, two retrospective studies that included over 2000 patients did not show any association between TIVA and longer survival. Also, data from an RCT (TIVA vs sevoflurane anesthesia) of patients undergoing breast cancer surgery could not demonstrate differences in 2 years recurrence-free and overall survival. However, survival was not the primary endpoint of the study, which also lacked significant statistical power.[125] Our group investigated differences in survival in patients receiving different volatile anesthetics during glioblastoma surgery.[136] We observed no association between the use of desflurane or isoflurane in progression-free and overall survival.[136]

The VAPOR-C trial (NCT04074460) is a RCT designed to investigate the effect of TIVA versus sevoflurane anesthesia on cancer recurrence in patients having surgery for lung or colorectal cancers.[143] The GA-CARES (NCT03034096) study is also a large clinical trial that will randomize patients to TIVA versus volatile anesthesia. The primary endpoint is all-cause mortality. Similar studies also being conducted in patients with pancreatic (NCT03447691) and breast (NCT02839668) cancers.

Conclusion

The perioperative period is a time of vulnerability for patients with cancer because it can promote the seeding of CTCs or the growth of micrometastatic tumors. The evidence from experimental laboratory studies demonstrates that anesthetics can modulate the metastatic behaviors of cancer cells. Anesthetics can also affect immune surveillance and inflammatory responses. Nevertheless, it is less clear about the actual clinical relevance of such changes in patients with cancer progression and patient's survival.

We think that the strength of evidence is weak to recommend the use of TIVA to improve cancer-related or overall survival after oncologic surgery. As for regional anesthesia, there is strong evidence to conclude that the impact of paravertebral blocks does not influence cancer recurrence after breast cancer surgery. The findings of ongoing and future randomized control trials will bring light on whether an anesthetic technique modifies the long-term survival of patients who had surgery for cancer.

Disclosure

The authors declare no conflicts of interest.

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