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Anesthetics or anesthetic techniques and cancer surgical outcomes: a possible link

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As of 2018 cancer is responsible for almost 9.6 million deaths annually and, with an aging population, the incidence of cancer is expected to continue to rise. Surgery is an important treatment modality for patients with solid organ cancers. It has been postulated that, due to potentially overlapping processes underlying the development of malignancy and the therapeutic pathways of various anesthetic agents, the choice of anesthetic type and method of administration may affect post-operative outcomes in patients with cancer. This is a literature review of the most recent evidence extracted from various databases including PubMed, EMBASE, and the Cochrane, as well as journals and book reference lists. The review highlights the pathophysiological processes underpinning cancer development and the molecular actions of anesthetic agents, pre-clinical and retrospective studies investigating cancer and anesthetics, as well as ongoing clinical trials. Overall, there are conflicting results regarding the impact of regional vs. general anesthesia on cancer recurrence, whilst the majority of data suggest a benefit of the use of intravenous propofol over inhalational volatile anesthetics. The biological changes associated with the surgical inflammatory response offer a unique opportunity to intervene to counteract any potentially cancer-promoting effects.

Keywords: Anesthesia; Anesthetics; Cancer; Neoplasms; Postoperative period; Surgery.

General introduction: anesthesia and cancer outcomes

Cancer was responsible for 9.6 million deaths worldwide in 2018 and is the second leading cause of mortality globally [1]. In the context of aging populations, the incidence of cancer is expected to continue to rise from 14 million in 2012 to an estimated 24 million in 2035 [2]. Surgery is a central treatment modality for patients with solid organ cancers; it is estimated that over 80% of cancer patients will undergo a surgical procedure as part of their treatment [3]. Recurrence of cancer after surgery is affected by numerous factors including primary cancer organ type, Tumor Node Metastasis staging, and surgical technique.

Surgery results in a complex inflammatory response involving both the innate and adaptive immune system and is thought to result in a period of postoperative immunosuppression that predisposes to infection [4]. The inflammatory response has wide ranging systemic effects from impacting postoperative recovery to sleep quality [4,5]. Perioperative interventions such as anesthesia and anesthetic techniques have been hypothesized to play a role in modifying the surgical inflammatory response and thus cancer recurrence. The role of anesthesia on cancer recurrence has been the subject of increasing attention over the past decade and has resulted in many retrospective studies and pre-clinical research into the area. An increasing body of pre-clinical laboratory data suggests that general anesthetic agents have the ability to influence key hallmarks of cancer involved in tumorigenesis and metastasis [6]. There are two key classes of general anesthetic agents used in clinical practice: intravenous propofol and inhalational volatile anesthetic agents such as sevoflurane. Inhalation anesthetics have been shown to enhance proliferation, migration, invasion, and angiogenesis across a range of cancer cell types, whereas propofol has been shown to antagonize these same pathways [6]. Several retrospective studies have demonstrated an association between inhalational anesthesia and reduced recurrence-free survival in cancer patients undergoing elective surgery compared to survival in cancer patients who receive propofol-based anesthesia [7,8]. However, there are smaller retrospective studies that show no association, highlighting the need for future prospective and randomized controlled trials.

In this literature review we present the most recent evidence extracted from various databases including PubMed, EMBASE, and the Cochrane, as well as journals and book reference lists.

Cancer development

Cancer results from the proliferation of a clonal population of cells—a multistage process termed carcinogenesis. A single cell undergoes a mutation in critical genes responsible for the control of cell division, cell death, and the maintenance of genetic integrity thereby rendering the cell susceptible to the acquisition of further mutations [9]. The tumor cell becomes refractory to regulatory biochemical cell signaling pathways, which results in the progressive loss of differentiation and in turn, uncontrolled cellular proliferation ensues [9]. The expanding pre-neoplastic cell clone outgrows the capacity of the host vasculature and subsequent tumor progression is dependent on angiogenesis for the supply of growth factors and oxygen [10]. Pro-angiogenic factors including vascular endothelial growth factor (VEGF), platelet-derived endothelial growth factor (PDGF), and fibroblast growth factor are released from the tumor, establishing a new capillary network that promotes tumor growth, local invasion, and metastasis [11].

Metastasis and tumor progression

The pathogenesis of cancer metastases is complex, of which a series of tumor-host interactions are outlined by the metastatic cascade. Tumor cells lose their cell polarity and cell-cell adhesion properties, allowing for a subclone of cells with metastatic potential to invade the surrounding stroma and dissociate from the primary tumor mass (invasion) [12]. The detached cells, known as circulating tumor cells (CTCs), enter the systemic circulation via the established blood vessel network formed through angiogenesis and the lymphatic system (intravasation). During this process, most CTCs are rapidly destroyed by the immune system as a result of host immunosurveillance carried out by NK cells and CD8+ T cells, with only 0.1% of cells viable after 24 h [13]. The surviving tumor cells arrest in the capillary beds of a distant organ and adhere to capillary endothelial cells and thus penetrate the endothelium and basement membrane (extravasation). Consequently, proliferation within the secondary organ parenchyma achieves metastasis and the formation of a malignant tumor.

It is becoming increasingly recognized that various anesthetic agents used in the perioperative setting for primary cancer surgery have a role in cancer recurrence through postoperative metastasis [14]. In this narrative review, we aim to present the current state of evidence linking anesthetic techniques and cancer surgical outcomes.

Molecular actions of anesthetics and cancer

Inhalational anesthetics

Volatile anesthesia

Rapidly acting volatile anesthetic agents, such as sevoflurane and isoflurane, are commonly used for the maintenance of general anesthesia. It is well-established that these agents have pro-inflammatory and immune modulatory effects, and therefore, may have deleterious effects in cancer recurrence, although the exact molecular mechanisms are incompletely understood [6,15,16].

In particular, volatile anesthetics have been shown to suppress NK cell cytotoxicity and induce T-lymphocyte apoptosis, of which both cells have a vital role in immune surveillance and achieving anti-metastatic immunity after cancer surgery [17,18]. Thus, volatile agents may promote immunosuppression and the metastatic spread of residual cancer cells postoperatively.

Moreover, volatile anesthetics have a protective role against ischemia-reperfusion injury in various organs and tissues [19]. These cytoprotective features, however, are associated with the upregulation of hypoxia-inducible factor 1-alpha (HIF-1α) in tumor cells, causing increased transcription of genes encoding VEGF and PDGF [20] and thereby facilitate tumor angiogenesis, residual cell survival, and tumor cell migration.

Nitrous oxide

Nitrous oxide is an anesthetic gas used for the maintenance of anesthesia often in combination with more potent general anes-

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thetic techniques for surgical anesthesia. This inhaled agent has been related to a number of immunosuppressive effects, primarily through impaired neutrophil chemotaxis and suppressed NK cell and macrophage function [21,22]. This is mediated by its interaction with vitamin B12, causing selective inactivation of methionine synthase, which is critical for DNA, purine, and thymidylate synthesis [23]. Consequently, there is impaired synthesis of hematopoietic cells involved in tumor surveillance.

Intravenous anesthetics

Propofol

Propofol is the most extensively used intravenous anesthetic agent for induction and maintenance of general anesthesia. It has been demonstrated to possess a range of antitumor properties and may seem to have protective effects against cancer cell dissemination and development of metastasis. This is achieved directly by regulating key cell signaling pathways implicated in tumorigenesis, such as the MAPK and NF-κB pathways [24], as well as regulating expression of miRNA and HIF-1α [24,25]. Indirectly, propofol has been shown to minimize perioperative immunosuppression by preserving NK cell and cytotoxic T cell function [26].

Ketamine and thiopental

Ketamine and thiopental are alternative suitable intravenous anesthetic agents indicated in emergency medicine and for patients with high intracranial pressure respectively. Both agents have exhibited immunomodulatory effects by suppressing NK cell activity and increasing tumor cell viability [27]. In particular, ketamine can upregulate anti-apoptotic proteins such as Bcl-2 enabling tumor cell proliferation and promotes production of pro-inflammatory cytokines such as IL-6 and TNFα [28,29].

Local anesthesia

Local anesthetics cause reversible, local inhibition of nociception, providing targeted anesthesia and analgesia. Local anesthetics have been shown to exert anti-tumor growth activity [30], although exact mechanisms are widely conflicted in studies. Possible mechanisms include their well-established inhibitory actions on voltage-gated sodium channels, which are expressed by cancer cells and correlate with tumor growth and metastatic formation [31]. Other evidence suggests these agents have protective effects on cell-mediated immunity and administration of lidocaine in particular can directly inhibit the epidermal growth factor receptor (EGFR) involved in cellular proliferation [30]. Intravenous infusions of lidocaine are a popular component of multimodal analgesia, particularly for major surgery, and therefore, are a feasible adjunct.

Sedatives

Common benzodiazepines, consisting of midazolam, lorazepam, and diazepam, are primarily used for preoperative sedation. The effect of benzodiazepines on tumor recurrence is disputed between studies. Early studies show that these sedatives, especially midazolam, have negative immunomodulatory effects and potentiate tumor occurrence [32]. Other studies report there is no association [33].

Opioids

Opioid analgesics are widely used in the perioperative period to supplement general anesthetic agents during induction and maintenance of anesthesia. Evidence from experimental studies investigating the role of opioids in tumor growth and metastasis is conflicting. Multiple animal studies have found that some opioids promote immunosuppression and in turn, tumor recurrence post-operatively, with the effects on immune function varying between the different types of opioids. In particular, morphine has largely been shown to suppress NK cell cytotoxicity and T-cell proliferation [34,35]; however, a small number of studies contradict these findings and instead propose the antitumor effects of morphine [36,37]. Likewise, fentanyl has been shown to inhibit NK cells and promote apoptosis of lymphocytes and macrophages in various laboratory studies [38,39]. Yet, a recent retrospective cohort study of 1,679 patients with stage I-III colorectal cancer showed no association between fentanyl and oncological outcomes/prognosis [40]. Alternatively, tramadol has been shown to have immune stimulatory properties by enhancing NK cell cytotoxicity [41].

There is also evidence that mu-opioid receptors (MORs) are overexpressed in certain cancers. Consequently, opioid binding at the MOR directly promotes cancer cell growth via growth-factor induced receptor signaling and potentiation of angiogenesis [42]. A study of lung samples from 34 patients with lung cancer demonstrated there was a two-fold increase in MOR expression in patients with metastatic lung disease [43]. Clinical studies further support the role of MOR in cancer progression. In a retrospective study of 113 prostate cancer patients, overexpression of MOR was associated with reduced overall survival and progression-free survival, especially prominent in those with metastatic disease [44]. In keeping with these results, two randomized controlled trials have shown treatment with Methylnaltrexone (a MOR antagonist) is associated with increased overall survival in end-stage cancer patients [45].

Overall, the role of opioids in facilitating tumor recurrence and metastasis are variable and conflicting with opioid type, dosage, and administration also influencing outcomes. Greater quality clinical evidence in the form of prospective randomized controlled trials is needed.

Pre-clinical *in vitro* and *in vivo* studies of cancer and anesthetics

The effects of anesthesia on various cancers have been extensively studied *in vitro*, although *in vivo* studies are limited in comparison. The molecular actions of anesthetic agents and lignocaine are summarized in Table 1. Understanding the underlying

Table 1. Summary of the Molecular Actions of Anesthetics Found in *in vitro* and *in vivo* Studies

Anesthetics	Oncological effects
Sevoflurane	Colon cancer cells:
	Induces apoptosis
	Inhibits proliferation and invasion as it inhibits Ras/Raf/MEK/ERK signaling pathway [46]
	Ovarian cancer cells:
	Inhibits migration and invasion
	↓ MMP-9 and STC1 [48]
	Inhibits proliferation via ↓ phosphorylation of JNK and p38 MAPK signaling pathways [49]
	Potential enhanced cancer proliferation via ↑ VEGF-A, MMP-11, CXCR2, and TGF-β genes [50]
	Cervical cancer cells:
	Enhanced proliferation, migration, and invasion of cells via ↑ histone deacetylase 6 expression via the ERK1/2 and phosphatidylinositide 3-kinase/AKT signaling pathways [52]
	Osteosarcoma cells:
	Inhibits invasion and proliferation via ↓ miR-203/WNT2B/Wnt/β-catenin axis [53]
	Leukemia cells:
	Inhibits proliferation via ↓ Wnt/β-catenin [54]
	Induces cognitive dysfunction via Wnt/β-catenin-Annexin A1 pathway [55]
	Lung cancer cells:
	Promotes metastases via ↑ IL-6 [56]
	Glioma cells:
	Inhibits growth via ↓ MMP-2 migration and activity [57]
Isoflurane	Hepatic carcinoma cells:
	Inhibits growth via NF-κB and PI3K/Akt signaling pathways [58]
	Glioblastoma cells:
	Promotes tumor and migration [59]
Propofol	Human colon cancer cells:
	Inhibits JAK2/STAT3 pathway
	Inhibits proliferation, migration, and invasion [60]
	Induces apoptosis via STAT3/HOTAIR by ↑ WIF-1 and ↓ Wnt pathway [61]
	Adenocarcinoma alveolar basal epithelial cells:
	Accelerates apoptosis via miR-21/PTEN/AKT pathway [62]
	Pancreatic cancer cells:
	Inhibits migration and induces apoptosis via miR-34a-mediated E-cadherin and LOC285194 signals [63]
	↓ expression of ADAM8
	Inhibits cell proliferation and migration via ↓ β1, ERK1/2, MMP2, and MMP9 [64]
	Human gastric cells:
	Inhibition of EMT, migration, and invasion [65]
	Papillary thyroid cancer cells:
	Inhibits proliferation and migration
	↑ miR-320a and ↓ ANRIL
	↓ Wnt/β-catenin and NF-κB [66]
	Glioma cells:
	Inhibits cell proliferation, invasion, and migration via mir-410-3p/TGFBR2 2 axis [67]
	Cardia cancer cells:
	Inhibits proliferation of cell growth
	Induces apoptosis via inhibition of the MAPK/ERK signaling pathway [68]

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Table 1. Continued

Anesthetics	Oncological effects
Lidocaine	Cervical cancer cells:
	Inhibits growth via modulation of IncRNA-MEG3/miR-421/BTG1 pathway [70]
	Lung cancer cells:
	Inhibits proliferation, migration, and invasion via ↓ TNFα, MMP-9 secretion, and ↓ GOLPH2 in NSCLC A549 cells [74]
	Retinoblastoma cells:
	Inhibits tumor growth via modulation of miR-520a-3p/EGFR axis [72]
	Human gastric cancer cells:
	Inhibits growth via altering MAPK pathway [73]

Ras/Raf/MEK/ERK: Ras/Raf/Mitogen-activated protein kinase/ERK kinase (MEK)/extracellular-signal-regulated kinase (ERK), MMP: Matrix metalloproteinase, STC1: stanniocalcin 1, JNK: c-Jun N-terminal kinase, p38 MAPK: p38 mitogen-activated protein kinase, VEGF-A: vascular endothelial growth factor-A, CXCR2: CXC chemokine receptor 2, TGF-β: Transforming growth factor beta, miR-203: microRNA-203, WNT: wingless-type MMTV integration site, IL: interleukin, NF-κB: Nuclear factor kappa B, PI3K: phosphatidylinositol 3-kinase, Akt: protein kinase B, JAK2: Janus kinase 2, STAT3: signal transducer and activator of transcription 3, HOTAIR: HOX transcript antisense RNA, WIF1: WNT Inhibitory Factor 1, PTEN: phosphatase and tensin homolog deleted on chromosome 10, ADAM8: A Disintegrin and metalloproteinase domain-containing protein 8, ERK: extracellular signal-regulated kinase, EMT: Epithelial-mesenchymal transition, ANRIL: antisense non-coding RNA in the INK4 locus, IncRNA: long non-coding RNA, BTG1: B-cell translocation gene 1, GOLPH2: Golgi phosphoprotein 2, NSCLC: non-small cell lung cancer, EGFR: epidermal growth factor.

mechanism of anesthetics and their potential effects on cell cycle arrest and apoptosis will give us more insight into the clinical implications.

Sevoflurane

Literature studying the effects of volatile anesthetics on cancer proliferation, migration, apoptosis, and tumor aggression remains inconsistent. Yang et al. [46] incubated SW480 colon cells with different concentrations of sevoflurane (1.7%, 3.4% and 5.1%) for 6 h, and the results have shown sevoflurane's capacity to induce apoptosis and inhibit the proliferation and invasion of colon cancer cells by inactivating the Ras/Raf/MEK/ERK signaling pathway. However, research by Bundscherer et al. [47] had revealed sevoflurane's and desflurane's limited effect on SW480 colon cancer cells, albeit at lower concentrations of drug during incubation (1% or 2.5% sevoflurane).

Sevoflurane was also found to inhibit the viability of SKOV3 and OVCAR3 cells in a dose-dependent manner, by reducing the migration and invasion ability of these cells. In addition, MMP-9 and stanniocalcin 1 (STC1) were also downregulated. These factors in combination have alluded to sevoflurane's involvement in inhibiting the progression of ovarian cancer (concentrations of sevoflurane ranging from 0.5% to 10%, depending on cell type) [48]. The effects of sevoflurane were corroborated in a study by Kang and Wang [49], which had also shown an inhibition of ovarian cancer proliferation (sevoflurane low concentration (1.7%), medium concentration (3.4%) and high concentration (5.1%) groups); however, this was through the repression of the phosphorylation of JNK and p38 MAPK signaling pathways. In contrast, a study that utilized higher concentrations of volatile anesthetics (sevoflurane 3.6%, isoflurane 2%, and desflurane 10.3%), but with a shorter incubation period, had revealed a significant increase in VEGF-A, MMP-11, CXCR2, and TGF-β genes, which collectively may enhance ovarian cancer proliferation [50]. Cervical cancer Caski and HeLa lines were incubated with sevoflurane (1–3%) for 2–4 h, which resulted in the proliferation, migration, and invasion of immortalized cervical cancer cells by increasing histone deacetylase 6 expression via the ERK1/2 and phosphatidylinositide 3-kinase/AKT signaling pathways [51,52].

Data from Chen et al. [53] has shown sevoflurane's inhibition of osteosarcoma cell invasion and proliferation through regulating miR-203/WNT2B/Wnt/β-catenin axis; cells were exposed to 0%, 1%, 2%, 5% and 10% sevoflurane. Further evidence of sevoflurane's involvement (0%, 2%, 4% or 8% sevoflurane) in the inhibition of Wnt/β-catenin is noted in the inhibition of leukemia cell proliferation [54], and involvement in cognitive dysfunction (3.6% sevoflurane) [55]. Furthermore, sevoflurane (0.2 mM) has been reported to promote lung metastases through the overexpression of IL-6 in pre-metastatic lung during the perioperative phase [56]. Results from Hurmath et al. [57] have highlighted that the inhibitory role of sevoflurane (2.5%), and different concentrations of thiopental, in glioma cells is dependent on regulating MMP-2 migration and activity. Another volatile anesthetic, isoflurane, has been shown to be involved in the inhibition of hepatic carcinoma aggression, as achieved through the regulation of NF-κB and PI3K/AKT signaling pathways [58], in addition to having detrimental effects in glioblastoma by promoting tumor and migration capacities (1.2% isoflurane) [59].

Propofol

A variety of mechanisms have been proposed to explain the role of propofol in cancer cells. Liang and Dong [60] incubated human colon cancer line SW480 with propofol (2, 4, and 8 μg/ml) and propofol with colivelin, which resulted in the inhibition of JAK2/STAT3 signaling pathway and the proliferation, migration, and invasion of human colon cancer cells. Similarly, Zhang et al. [61] incubated LOVO and SW480 cells with propofol (8 μg/ml), exerting an inhibition of cell invasion and induction of apoptosis through STAT3/HOTAIR by activation of WIF-1 and the suppression of the Wnt pathway.

The A549 cancer line, which are adenocarcinoma alveolar basal epithelial cells, was incubated with propofol (0, 2, 5, and 10 μg/ml). Propofol demonstrated inhibition of A549 cell growth in a concentrated and time-dependent manner, by accelerating apoptosis via the miR-21/PTEN/AKT pathway [62]. Wang et al. [63] exposed pancreatic cancer PANC-1 cells to a relatively higher concentration of propofol (20 μg/ml). Consequently, propofol was seen to inhibit the migration and apoptosis induction of PANC-1 cells via miR-34a-mediated E-cadherin and LOC285194 signals. In another study, PANC-1 cells were treated with 5 or 10 μg/ml of propofol, resulting in a reduced expression of ADAM8 and inhibition of cell proliferation and migration of PANC-1 via downregulation of β1, ERK1/2, MMP2, and MMP9 [64]. Human gastric cells, SGC-7901 and NCI-N87, were exposed to different concentrations of propofol (5, 10, 20 μM), in which inhibition of epithelial to mesenchymal transition, migration, and invasion of gastric cells were noted in a dose-dependent manner [65]. The inhibitory effects of propofol (5, 10, 20 mg/ml) on papillary thyroid cancer cells were reported, in which an upregulation of miR-320a and downregulation of ANRIL and inactivation of Wnt/β-catenin and NF-κB pathways all played a role [66].

U251 and A172 glioma cell lines were incubated with different concentrations of propofol (5, 10 μg/ml) for 24 h. This consequently resulted in the inhibition of cell proliferation, invasion, and migration through the mir-410-3p/transforming growth factor-β receptor type 2 axis [67]. Finally, Su et al. [68] utilized higher concentrations of propofol (12.5, 25, and 50 μg/ml) in their incubation of cardia cancer cells and had reported an inhibition of proliferation of cancer cell growth and induction of apoptosis via inhibition of the MAPK/ERK signaling pathway. Our group has shown that propofol (4 μg/ml) reduced cell viability and inhibited proliferation migration and invasion of lung cancer cells, but not in neuroglioma cells. In lung cancer cells, propofol downregulated glucose transporter 1, mitochondrial pyruvate carrier 1, p-Akt, p-Erk1/2, and HIF-1α, and upregulated pigment epithelium derived factor expression [69]. The reason for the disparity in behavior of lung cancer cells and neuroglioma cells from our experiments is uncertain and warrants further study.

Lidocaine

Lidocaine, a local anesthetic, has also been investigated for its role in cancer involvement. For instance, lidocaine (50, 100, 500 or 1000 μM) was shown to inhibit cervical cancer growth through the modulation of the IncRNA-MEG3/miR-421/BTG1 pathway [70]. The large-cell cancer line, 95D, was exposed to different concentrations of lidocaine (2, 5, and 10 μg/ml). In a dose-dependent manner , lidocaine demonstrated anti-tumor activity by inhibiting the PI3K/AKT/mTOR signaling pathway [71]. Lidocaine (50, 100, 500 or 1000 μM) has been seen to also inhibit the growth of retinoblastomas by modulation of the miR-520a-3p/EGFR axis [72] and human gastric cancers by alteration of the MAPK pathway [73].

Overall, current literature does indicate a possible association between anesthetics and anti-tumor properties [74]. Although this may provide us with potential clinical implications, we must be cautious in any interpretation as there are considerable discrepancies in the methodologies between studies. This can be ultimately reduced to different concentrations of anesthetic drugs and varying length of incubation time.

Retrospective studies

Numerous retrospective clinical studies have investigated the potential relationship between anesthetic technique and the outcomes of patients following oncological surgery. As surgical stress is thought to produce a pro-inflammatory response that favors tumor growth and metastasis, optimizing perioperative interventions, including anesthesia, may confer an improvement in long-term cancer outcomes. Furthermore, surgical resection in patients with solid tumors can lead to tumor cell release into the circulation [75,76].

There is a significant lack of prospective evidence regarding the putative relationship between anesthetic technique and post-operative outcomes in oncological surgery. The only such randomized controlled trial studied the efficacy of regional paravertebral anesthesia in combination with propofol-based total intravenous anesthesia (TIVA) vs. sevoflurane inhalational anesthesia plus opioid analgesia [77]. The study was conducted in thirteen countries and recruited 2,100 women due for primary breast cancer surgery. The authors found that propofol anesthesia with paravertebral block had no impact breast cancer recurrence compared

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with inhalational anesthesia and opioids (HR: 0.97, 95% CI: 0.74, 1.3; P = 0.84) [77]. As the first and potentially largest RCT of its kind, these findings are pivotal, particularly in the context of the significant amount of retrospective evidence purporting a relationship between the use of TIVA and an improvement in post-operative survival and disease recurrence compared to inhalational anesthesia.

Wigmore et al. [7] conducted the largest retrospective series of 7,030 patients over a 3-year period from one cancer center, with around half of the patients receiving TIVA with propofol and the remainder receiving volatile inhalational anesthesia.

The hazard ratio (HR) for death within the inhalational cohort compared to the TIVA cohort was 1.46 (95% CI: 1.29, 1.66; P < 0.001), after multivariable analysis of known confounders and a median follow-up of 2.6 years. Furthermore, within the inhalational cohort, 87.9% of patients survived at one year, compared to 94.1% in the TIVA cohort. The authors found that the decreased survival within the inhalational group was present regardless of American Society of Anesthesiologists grade, surgical severity, or the presence of metastases at the point of operation.

These findings are supported by similar studies. Using data from a Swedish database, a retrospective study of 2,838 patients who received surgery for colon, rectal, or breast cancer found that the survival rate for patients in the propofol group was 4.7% higher at one year and 5.6% higher at five years compared to patients receiving volatile inhalational anesthesia [78]. It is important to note that the differences in this study were not significant after adjustment for confounders. An additional retrospective observational study of 922 patients who underwent esophagectomy found the inhalational anesthesia cohort had reduced overall survival (HR: 1.58, 95% CI: 1.24, 2.01; P < 0.001) and recurrence-free survival (HR: 1.42, 95% CI: 1.12, 1.79; P = 0.003) after multivariate adjustment. Similar favorable long-term outcomes with propofol–TIVA have also been found in patients undergoing gastrectomy [79] and colectomy [80].

Overall, it seems unclear whether tumor type plays a critical role in this apparent correlation; evidence suggests that the degree of surgical stress is an important determining factor. This theory seems to be supported by a retrospective analysis of 383 patients receiving modified radical mastectomy, rather than commoner and less invasive breast-conserving procedures, which found a statistically significant decrease in cancer recurrence in the group that received propofol-based TIVA (HR: 0.550, 95% CI: 0.311, 0.973; P = 0.037) [81]. However, there was no difference in overall survival between the propofol-based TIVA group and the sevoflurane group, and the study did not directly compare the outcomes of patients receiving mastectomy compared to those having breast-conserving surgery [81].

Despite the various studies that seem to suggest improved outcomes in patients receiving TIVA, it is important to note that there is a limited amount of prospective evidence, whilst the only RCT conducted suggests no benefit in post-operative outcomes with TIVA [77]. Furthermore, other retrospective studies have also reported no benefit in overall survival in patients receiving intravenous anesthesia for breast [78,82,83], lung [84], and colorectal surgery [78].

With regards to regional anesthesia, early, predominantly retrospective studies suggest that the use of regional anesthesia is associated with an improvement in overall and disease-free survival for colorectal, prostate, breast, ovarian, and head and neck malignancies [85–88]. Furthermore, a randomized trial of 177 patients with colorectal cancer demonstrated a benefit associated with epidural analgesia, but this was limited to 1–5 years post-operatively [89]. A randomized study of 132 patients with cancer of abdominal organs treated with abdominal surgery receiving epidural analgesia showed a non-statistically significant improvement in recurrence-free survival, although the study was clinically underpowered [90]. Although the precise reasons for this benefit remain to be elucidated, it has been postulated it may be due to the avoidance of opioids, which have previously been shown to potentiate tumor cell survival and angiogenesis [7,91].

Despite this, post-hoc analyses of previous clinical studies, as well as randomized trials, suggest that there is limited benefit associated with regional anesthesia in the context of oncological surgery. Reanalysis of the MASTER trial is the first and largest post-hoc analysis of nearly 500 patients who had abdominal malignancy who were randomized to general anesthesia or epidural anesthesia. The study demonstrated no significant impact of epidural anesthesia on the recurrence of cancer [92]. Additionally a recent large multi-country randomized controlled trial investigating the impact of regional anesthesia-analgesia (paravertebral blocks and propofol) or general anesthesia (sevoflurane) and opioid analgesia on local or metastatic breast cancer recurrence in 2,132 women found no difference between the two groups (HR for regional anesthesia: 0.97, 95% CI: 0.74, 1.28; P = 0.84) [77].

In conclusion, studies investigating the relationship between regional anesthesia, cancer recurrence, and overall survival have yielded mixed results, with many studies suggesting no benefit [85,86]. The results of clinical studies investigating propofol-based TIVA versus inhalational anesthesia are summarized in Table 2. However, the heterogeneous, non-randomized, retrospective natures of the majority of these studies are key limiting factors.

Table 2. Summary of the Clinical Studies Evaluating Relative Benefit of Propofol-based TIVA vs. Inhalational Anesthesia on Cancer Recurrence and Overall Survival

Study type	Anesthesia	Cancer type	Results
Randomized controlled trial [77]	Inhalational anesthesia plus opioids vs. propofol-based TIVA	Breast	Propofol-based TIVA had no impact on breast cancer recurrence compared with inhalational anesthesia and opioids: HR 0.97 (95% CI: 0.74, 1.3; P = 0.84)
Retrospective analysis [7]	Inhalational anesthesia vs. propofol-based TIVA	Solid organ	Inhalational anesthesia associated with greater HR of death: HR 1.46 (95% CI 1.29, 1.66; P < 0.001)
Retrospective analysis [78]	Inhalational anesthesia vs. propofol-based TIVA	Breast, colorectal	Differences in overall one- and five-year survival rates for all three sites combined were 4.7% (P = 0.004) and 5.6% (P < 0.001), respectively, in favor of propofol.
Retrospective analysis [79]	Inhalational anesthesia vs. propofol-based TIVA	Gastric	TIVA was associated with a HR of 0.67 (95% CI: 0.58, 0.77) for death in univariate analysis and 0.65 (95% CI: 0.56, 0.75) after a multivariate analysis of known confounders in the matched group.
Retrospective analysis [80]	Inhalational anesthesia vs. propofol-based TIVA	Colon	(HR: 0.22, 95% CI: 0.11, 0.42; P < 0.001) or higher tumor-node-metastasis stage (HR: 0.42, 95% CI: 0.32, 0.55; P < 0.001) and presence of metastases (HR: 0.67, 95% CI: 0.51, 0.86; P = 0.002) or absence of metastases (HR: 0.08, 95% CI: 0.01, 0.62; P = 0.016)
Retrospective analysis [81]	Inhalational anesthesia vs. propofol-based TIVA	Breast	Propofol group showed a lower rate of cancer recurrence (P = 0.037), with an estimated HR of 0.550 (95% CI: 0.311, 0.973).
Retrospective analysis [82]	Inhalational anesthesia vs. propofol-based TIVA	Breast	No association found using Cox regression analyses and propensity matching.
Retrospective analysis [83]	Inhalational anesthesia vs. propofol-based TIVA	Breast	Kaplan-Meier survival curves showed no significant difference in recurrence-free or overall survival between the two groups.
Retrospective analysis [84]	Inhalational anesthesia vs. propofol-based TIVA	Lung	No significant difference in HR for recurrence (P = 0.233) or HR for death (P = 0.551) between the two groups.

TIVA: total intravenous anesthesia, HR: hazard ratio.

Ongoing clinical trials

As discussed previously, evidence regarding the effects of various anesthetic techniques on surgical outcomes in patients with cancer is almost exclusively from observational, retrospective studies. The single RCT that has been conducted suggests regional anesthesia is unlikely to impact recurrence after breast cancer surgery; other tumor types may show a difference based on anesthetic technique [77]. Furthermore, an interesting new pre-clinical development suggests that peri-operative systemically administered lidocaine decreases pulmonary metastases when combined with inhalational anesthesia, thus potentially heralding a new avenue for clinical trial development [93].

There are a several large, randomized controlled trials investigating the effect of inhalational anesthetic agents vs. propofol on cancer recurrence following surgery. Results from these trials are eagerly awaited and will be highly informative in providing high quality evidence to answer and provide greater certainty as to the impact of anesthetic choice on cancer recurrence (NCT01975064 [94], NCT02660411 [95], NCT03034096 [96], ACTRN12617001065381 [97], NCT02660411 [98]).

Implications and conclusions

There is an increasing body of evidence investigating the impact of anesthesia and anesthetic techniques on cancer recurrence and survival in cancer patients. The impact of regional anesthesia vs. general anesthesia on cancer recurrence is also uncertain, with conflicting results from retrospective studies and small clinical trials. A recent large multi-country randomized controlled trial failed to show a benefit of regional anesthesia on either local or metastatic recurrence of breast cancer following surgery [77]. Further studies are required across a greater range of cancer types and more diverse patient populations to definitively prove any

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benefit of regional over general anesthesia on postoperative cancer recurrence.

The majority of evidence thus far suggests a benefit of the use of intravenous propofol over inhalational volatile anesthetics such as sevoflurane. This evidence is mainly pre-clinical and retrospective in nature. A recent meta-analysis that examined the effect of propofol vs. volatile anesthesia on cancer recurrence and survival found the use of propofol-based TIVA was associated with improved recurrence-free survival in all cancer types (pooled HR: 0.78, 95% CI: 0.65, 0.94; P < 0.01) and improved overall survival (pooled HR: 0.76, 95% CI: 0.63, 0.92; P < 0.01) [99]. Although this provides support that propofol is superior to volatile anesthesia in reducing cancer recurrence, the meta-analysis has several limitations. Notably nine of the ten studies included were observational studies, and heterogeneity in studies included in terms of study population, the stages of cancer and differences in use of regional anesthesia. Therefore, the results of four large randomized controlled trials investigating this question will be eagerly anticipated and will provide more definitive results as to whether propofol is superior to volatile anesthesia .

The perioperative period is characterized by physiological changes induced by surgery and perioperative interventions. These biological changes associated with the surgical inflammatory response, and the pharmacological actions of anesthetic drugs, may promote the recurrence of cancer in postoperative cancer patients. This highlights an opportunity to intervene to counteract any potentially cancer-promoting effects. Anesthesia, anesthetic technique, and other strategies such as the use of anti-adrenergic, anti-inflammatory, and anti-thrombotic therapies (which haven't been discussed in this review) offer the potential to promote recurrence-free survival of postoperative cancer patients [6,100].

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Azeem Alam (Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing)
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