

Anesthesia and cancer recurrence: a narrative review

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Cancer is a leading cause of death worldwide. With the increasingly aging population, the number of emerging cancer cases is expected to increase markedly in the foreseeable future. Surgical resection with adjuvant therapy is the best available option for the potential cure of many solid tumors; thus, approximately 80% of patients with cancer undergo at least one surgical procedure during their disease. Agents used in general anesthesia can modulate cytokine release, transcription factors, and/or oncogenes. This can affect host immunity and the capability of cancer cells to survive and migrate, not only during surgery but for up to several weeks after surgery. However, it remains unknown whether exposure to anesthetic agents affects cancer recurrence or metastasis. This review explores the current literature to explain whether and how the choice of anesthetic and perioperative medication affect cancer surgery outcomes.

Keywords: Anesthesia; Cancer recurrence; Opioid analgesics; Propofol; Volatile anesthetics.

INTRODUCTION

Today, the biology and treatment of cancer are better understood than ever before, but cancer remains the leading cause of death, with its number continuously increasing as the population ages [1-3].

Surgical resection with adjuvant therapy is the best available option for the potential cure of many solid tumors; thus, approximately 80% of patients with cancer undergo at least one surgical procedure during their disease [4].

However, even with the best technique, incomplete resection margins or iatrogenic “seeding” of tumor cells with surgical manipulation can lead to a fraction of cancer cells remaining in the body. Some patients develop micrometastases at the time of surgery [5-10]. Whether the remaining cancer cells lead to recurrence and distant metastases depends on the balance between the tumor’s capability to seed, pro-

liferate, and promote angiogenesis and the anti-metastatic immunity of the host [11-13].

To date, numerous *in vitro*, *in vivo* and retrospective studies have shown that anesthetics, opioids, and other perioperative medications influence cancer cell activity and survival, either directly and indirectly, through altering the neuroendocrine stress response to surgery, cancer cell signaling, and the host immunity [2,7,14-54].

This review reports the latest data regarding the influence of anesthetic agents on cancer recurrence and metastasis. To date, there are no official recommendations for the best anesthetic for patients with cancer. However, some anesthetic agents may increase this risk, whereas others may reduce it.

To explore how anesthesia can affect cancer progression, I will briefly present tumor biology, potential targets for cancer control, and the effects of various commonly used anes-

thetics on various cancers.

BASIC TUMOR BIOLOGY

Recurrence and metastatic transition occur via three basic mechanisms [55,56]. Local recurrence occurs when surviving cancer cells proliferate at the resection site through the activation of proinflammatory cytokines, pro-oncogenes, and angiogenic factors. Second, the cancer cells were seeded during surgical manipulation. Third, cancer cells transform and gain the capability to migrate to distant sites via vascular or lymphatic spread through the activation and mutation of oncogenes.

Multiple perioperative factors create a tumorigenic environment, and surgery produces intense stress and inflammation because of tissue damage through the activation of neural and inflammatory signaling pathways. The physiological stress response to surgery causes immunosuppression through the release of various hormonal mediators such as catecholamines, prostaglandins, and growth factors [57]. The release of cortisol, catecholamines, and cytokines (such as interleukin-6 [IL-6] and prostaglandins such as prostaglandin E_2 [PGE₂]) suppresses the function of immune cells, including natural killer (NK) cells, which are the primary defense against cancer, and CD8+ T cells. In addition, pro-oncogenic cell lines, regulatory T cells, and type 2 helper T cells are activated and proliferated [14,58]. Prostaglandins and catecholamines can activate β 2-adrenergic [59] and cyclooxygenase-2 receptors [60] that may help metastasis.

Tissue hypoxia at the site of injury upregulates hypoxia-inducible factor 1 α (HIF-1 α), which promotes cell proliferation, angiogenesis, and metastasis [61]. HIF-1 α confers a survival advantage to tumor cells [18,62-64] and stimulates tumor growth by triggering vascular endothelial growth factor (VEGF) [65], which accelerates angiogenesis [66] and can promote remodeling of lymphatics for metastasis [67]. This may cause local tumors to metastasize, which is referred to as epithelial-to-mesenchymal transition [68]. This proinflammatory and immunosuppressive phenomenon usually persists for up to 1 week after surgery [69]. However, its duration may extend beyond 1 week depending on the surgical stress [39,57].

Therefore, it is logical to believe that anesthesiologists use the sympatholytic, anti-inflammatory, and immunomodulatory effects of various anesthetics to inhibit cancer progression and improve patient outcomes. Ideally, anesthetics

should 1) attenuate inflammation, 2) promote NK and CD8+ cell activity, and 3) attenuate the transcription factors and oncogenes that promote cancer cell survival and metastasis.

VOLATILE VS. PROPOFOL-BASED TOTAL INTRAVENOUS ANESTHESIA (TIVA)

Numerous laboratory studies showed that volatile anesthetics may enhance metastasis by directly promoting cancer cells and inhibiting immune cells [34,70-72]. In contrast, many preclinical studies have suggested that propofol has antitumor effects and prevents perioperative immune suppression through its anti-inflammatory and antioxidant actions [73]; in vitro and in vivo studies have shown that volatile anesthetics directly impair macrophages, dendritic cells, neutrophils, T-cells, and NK cells. Volatile anesthetics also upregulate HIF-1 α , VEGF, insulin-like growth factor 1, and phosphoinositide 3-kinase-Akt pathway (PI3K-Akt pathway) and have anti-apoptotic effects. All of these factors can accelerate the proliferation and metastasis of minimally invasive cancer cells [33,37,61,69,70,74]. Exposure of breast, ovarian, and kidney cancer cells to volatile anesthetics increases IL-1/6/8 and tumor necrosis factor (TNF), suppresses NK and T-cells, and increases angiogenic and migration factors [3,16,75-77]. A 2016 systematic review of multiple in vivo studies found that volatile anesthetics are associated with an increased incidence of metastasis [78]. In contrast, propofol shows antitumor effects by directly regulating key ribonucleic acid pathways and signaling in laboratory studies [79]. Propofol inhibits the proliferation, invasion, and migration of gastric cancer cell lines [80]. In non-small cell lung cancer (NSCLC), propofol reduced cancer cell migration and invasion by inhibiting HIF-1 α [81]. Propofol reduces the expression of neuroepithelial cell transforming gene 1, which increases the migration of breast cancer cell lines [72] and accelerates cell apoptosis through the miR-24/p27 pathway [82]. Propofol decreases the expression of the sex-determining region Y-box (SOX4) gene [83,84], which is associated with poor prognosis in endometrial and esophageal squamous cell carcinoma cells [85].

In an animal model of breast cancer, propofol did not increase metastasis or inhibit NK cell activity, whereas halothane did [31]. In another breast cancer model, propofol reduced lung metastasis compared with sevoflurane [86]. Excised breast cancer specimens from patients who received propofol with a paravertebral block showed increased NK cell infiltration into breast cancer tissue compared to pa-

tients who received volatile anesthetics [71]. A small study of head and neck cancer resection found that expression of HIF-1 α was increased in patients who received volatile anesthetics [87]. Serum from patients who received the regional combined propofol technique for colon cancer resection inhibited the proliferation and invasion of cultured colon cancer cells and showed a higher rate of cell apoptosis than that from patients who received volatile/opioid technology [88]. In another study of breast cancer surgery, application of serum from females who received propofol with paravertebral blocked anesthesia preserved NK cell activity and increased cancer cell apoptosis compared to that from females who received sevoflurane/opioid anesthesia [34,35]. In a meta-analysis, *in vitro* and translational data showed that volatile anesthetics are potent immunosuppressive and tumorigenic agents that promote metastasis, whereas propofol is anti-inflammatory and anti-tumorigenic and prevents metastasis [89].

An important question is whether the known effects of volatile anesthetics have been clinically demonstrated *in vitro* or *in vivo*. Most retrospective clinical studies comparing propofol with volatile anesthetics have reported conflicting results. Some studies have shown a beneficial effect of TIVA compared to volatile anesthetics, while others have shown no difference [40-42,45,47,49,90-93].

Wigmore et al. [41] conducted a retrospective propensity score-matched cohort analysis ($n = 7,030$) on patients who underwent various types of cancer surgery. Overall survival was improved in patients administered propofol rather than volatile anesthesia (15.6% vs. 22.8% 5-year mortality after surgery; hazard ratio [HR], 0.68; 95% CI, 0.60 to 0.78; $P < 0.001$). These findings are in line with those of other retrospective studies that have shown improved overall survival with TIVA in esophageal ($n = 922$) [44], gastric ($n = 2,856$) [43], and colon ($n = 1,363$) [94] cancer surgery. A meta-analysis based primarily on retrospective single-institutional series repeatedly found that TIVA was associated with increased disease-free and overall survival in many solid tumors [89]; these associations were stronger when surgery was longer, surgical trauma was more severe, and malignancy was more aggressive [89]. A 2019 meta-analysis from five retrospective studies and one small randomized controlled trial ($n > 7,800$, breast, esophageal, or NSCLC surgery) reported that the use of TIVA was associated with improved recurrence-free survival compared to volatile anesthesia (pooled HR, 0.78; 95% CI, 0.65–0.94) [95]. Enlund et al. [93] identified all patients ($n = 6,305$) who received anesthesia

for breast cancer surgery in the Swedish Breast Cancer Quality Register between 2006 and 2012. In the final model, the 5-year survival rates in the propofol and sevoflurane groups were 91.0% and 81.8%, respectively ($P = 0.126$). However, the results ranged from ‘non-significant’ to a ‘proposed’ and even ‘determined’ difference in survival, with propofol having up to 9.2% higher 5 year survival rate than sevoflurane (HR, 1.46; 95% CI, 1.10–1.95) depending on the statistical adjustment method used [93]. A retrospective Danish database analysis ($n > 8,600$, propensity-score matched) showed a slight increase in cancer recurrence with volatile anesthetic use compared with TIVA in patients undergoing colorectal cancer surgery (HR, 1.12; 95% CI, 1.02–1.13) but no difference in overall survival [46].

However, different results have been obtained. In a retrospective study, Yoo et al. [45] reported no benefit in cancer recurrence and overall survival with TIVA compared with volatile anesthesia in breast cancer surgery ($n = 5,331$). These results are in line with those of other retrospective studies that reported no difference in overall survival for breast ($n = 2,645$ [96] and $n = 1,217$ [90]), colorectal ($n = 1,297$) [90], lung ($n = 943$) [91], and oral cancer surgery ($n = 604$) [97]. This may be supported by some preclinical and clinical studies suggesting that volatile anesthetics have no effect on cancer cells or rather have an inhibitory effect. Sevoflurane arrested the cell cycle in the G1 phase and inhibited the proliferation of breast cancer cells [98]. Volatile anesthetics increase the chemosensitivity to cisplatin (a chemotherapeutic agent) [77] and suppress the growth and migration [99] of NSCLC cells. During breast cancer resection, the release of VEGF-C did not differ between TIVA and sevoflurane anesthesia [100]. A randomized trial of breast cancer ($n = 210$) found similar numbers of circulating tumor cells in the blood of patients after anesthesia with sevoflurane and propofol [51]. Among patients undergoing breast cancer surgery, the expression of regulatory T-cell enzymes that promote cancer recurrence did not differ between the patients who received volatile anesthesia and those who received TIVA [101]. In a randomized trial of colorectal cancer ($n = 153$), sevoflurane and propofol anesthesia resulted in similar fractions of circulating NK, helper T, and cytotoxic T cells after surgery [102]. In a meta-analysis of clinical studies, inflammatory biomarkers (IL6, IL10, TNF- α , and C-reactive protein [CRP]) did not differ between TIVA and sevoflurane anesthesia groups [103].

Large randomized clinical trials are needed because of the heterogeneity associated with surgical scope, cancer type,

and patient characteristics, as well as other limitations associated with the retrospective nature of most previous studies. Only one large randomized trial has been published, the Cancer and Anesthesia Study (CAN NCT01975064), which evaluated the survival of patients with breast cancer after exposure to general anesthesia ($n = 1,670$) [52]. Overall survival did not differ between the TIVA and sevoflurane anesthesia groups. Five year survival was 773/841 (91.9% [95% CI, 90.1–93.8]) in the TIVA group and 764/829 (92.2% [90.3–94.0]) in the sevoflurane group, (HR, 1.03; 95% CI, 0.73–1.44, $P = 0.875$). Thus, TIVA did not increase overall survival compared to sevoflurane anesthesia. Another large multicenter trial by Sessler et al. [53] compared regional (paravertebral block/propofol sedation) and general (sevoflurane) anesthesia in patients with breast cancer ($n = 2,132$). Regional anesthesia with propofol sedation did not reduce breast cancer recurrence at a median follow-up of 3 years when compared to general anesthesia with sevoflurane [HR, 0.97; 95% CI, 0.74–1.28; $P = 0.84$]. However, the study design was primarily a comparison between regional and general anesthesia and allowed for supplemental low-dose sevoflurane in the case of insufficient analgesia or sedation in the regional anesthesia group, potentially obscuring the differences between the two groups.

The two previous randomized trials had event rates (death or recurrence) of only 10%, given the relatively large expected differences in outcomes related to the anesthetic regimens (a 5% difference in overall survival [52] and a 30% reduction in cancer recurrence [53] in 1,670 and 2,132 patients, respectively); the statistical power may have been inadequate in these two studies. Additionally, the results of randomized controlled trials conducted on breast cancer may not be related to other cancer types. The potential of anesthetic agents to modify tumor biology, including local recurrence and metastasis, may vary substantially among cancer types [54]. Breast cancer resection procedures tend to be brief and have a commensurately low exposure to anesthetic drugs. Furthermore, the superficial location of these tumors may facilitate convenient surgical management with a low risk of cancer cell dissemination. Therefore, additional clinical trials are needed to evaluate the potential benefits of TIVA in patients undergoing major surgery.

Currently, a multicenter study is in progress comparing TIVA with volatile anesthetics for various major cancer surgeries (lobectomy or pneumonectomy, esophagectomy, radical cystectomy, pancreatectomy, partial hepatectomy, hyperthermic intraperitoneal chemotherapy, gastrectomy,

cholecystectomy, or bile duct resection; $n = 1,804$), with all-cause mortality as the primary outcome (NCT03034096). The aforementioned CAN trial includes another arm of patients undergoing primary resection of colorectal cancer and is currently in progress [104]. Another upcoming Volatile Anesthesia and Perioperative Outcomes Related to Cancer trial (VAPOR-C trial) is a large randomized trial that began in 2021. This trial is scheduled to be completed by 2025 for patients with lung or colorectal adenocarcinomas. This trial had a 2×2 factorial design comparing propofol and sevoflurane anesthesia with or without intravenous lidocaine (NCT04316013) [105].

OPIOIDS

Laboratory studies have identified three mechanisms through which opioids affect metastasis and tumor growth. Preclinical studies have shown that opioids have immunosuppressive properties, including impairment of neutrophil chemotaxis and reduction in NK cell cytotoxicity [106,107]. Opioids inhibit lymphocytes and mononuclear phagocytes via opioid or non-opioid receptors, such as toll-like receptor 4 [108]. In rectal cancer resection, the administration of morphine or oxycodone reduced the number of NK cells and T lymphocytes 12 h after injection [109]. Patients with breast cancer who received sevoflurane and opioids had reduced NK cell cytotoxicity [34] and a higher neutrophil-lymphocyte ratio, which is related to an increased risk of recurrence and poor outcome [110], compared to patients who received propofol and regional anesthesia. In pathological samples of resected breast cancer tissue, patients who received propofol/paravertebral anesthesia showed more infiltration of NK cells into their cancer tissue than patients who received general anesthesia with opioid analgesics [71]. However, these clinical studies used combined anesthetic techniques (such as sevoflurane versus opioids versus regional analgesia), making it impossible to determine the effects of opioids alone.

Second, opioids may directly affect cancer cells by activating various transcription factors [111] including VEGF receptors [100,112,113]. However, the most peculiar feature is the overexpression of the mu-opioid receptor (MOR) [108,114,115] on the surface of certain cancer cell lines that are activated by opioids [116–118]. In lung cancer, MOR expression is doubled in patients with metastatic disease compared to that in patients without metastases in tissue biopsy specimens [117]. In prostate cancer, MOR overexpression is

associated with decreased overall and progression-free survival [119]. In breast cancer, MOR gene polymorphisms reduced cancer-related mortality over a 10-year follow-up [120]. Consistent with this finding, the MOR antagonist methylnaltrexone has shown beneficial effects in stopping cancer progression. A post hoc analysis of two randomized clinical trials showed that methylnaltrexone, administered for opioid-induced constipation, was associated with improved overall survival in patients with advanced cancer [121]. When NSCLC cell lines were treated with methylnaltrexone, cancer invasion was inhibited [122]. Patients administered mu-opioid receptor antagonists such as naloxone showed improved survival in colorectal and breast cancers [111,113,123].

Third, opioids can interact with inflammatory cytokines (IL1, IL4, IL6, and TNF), which also control gene expression in the MOR [17,124-126].

However, other studies reported contradictory results. Morphine showed antitumor and antimetastatic effects in a mouse model of breast cancer [127-129]. Methadone also showed antitumor effects in glioblastoma [130] and leukemia models [131]. One study showed that morphine suppressed cancer cell proliferation by binding to the opioid growth factor receptor (OGFR) on the surface of lung cancer cell lines [132].

However, clinical studies have yielded contradictory results. A retrospective study of about 2800 patients undergoing surgery for renal cell carcinoma found that higher opioid doses during surgery were associated with decreased recurrence-free (HR, 1.06 per 10 MME; 95% CI, 1.03-1.09) and overall survival (HR, 1.05 per 10 MME; 95% CI, 1.02-1.09) [133]. Another retrospective study involving around 900 patients with NSCLC found that higher fentanyl doses during surgery were associated with decreased overall survival in patients with early stage cancer. However, this approach is not applicable for more advanced cancer [134]. However, another study on NSCLC (n = 1,000) found that increased intraoperative opioid use was not associated with increased recurrence or death [135]. Similarly, in patients undergoing colorectal cancer resection (n = 1,680), the amount of intraoperative fentanyl was not associated with recurrence or overall survival [136]. For breast cancer tissue resected from triple-negative breast cancer (n = 1,100) [137], higher intraoperative opioid doses were associated with improved recurrence free survival (HR, 0.93; 95% CI, 0.88-0.99; per 10 morphine milligram equivalent (MME) increase). A systematic review published in 2018 could not draw conclusions on

the relationship between perioperative opioid use and cancer recurrence in colorectal cancer because of inconsistent results and low-quality data [138].

There is no clinical evidence indicating that opioid-sparing techniques affect cancer outcomes. A follow-up analysis of data from a large randomized trial (n = 1,700+) of major abdominal or thoracic surgery found similar overall and recurrence-free survival rates at the 5-year follow-up between patients who received epidural/general anesthesia and those who received only general anesthesia with postoperative opioid analgesia [139]. In a randomized trial (n = 400, video-assisted thoracoscopic surgery for lung cancer), patients who received general anesthesia with postoperative opioid analgesia had similar recurrence-free and overall survival rates to those who received general/epidural anesthesia with postoperative epidural analgesia [140]. Sessler et al. [53] compared regional (paravertebral block with propofol sedation) and general (sevoflurane) anesthesia in patients with breast cancer in a larger multicenter trial (n = 2,132). Regional anesthesia with propofol sedation which used lower opioids, did not reduce breast cancer recurrence when compared with general anesthesia with sevoflurane/opioid at a median follow-up of 3 years [HR, 0.97; 95% CI, 0.74-1.28; P = 0.84]. These study designs make it difficult to isolate the pure effect of opioids on cancer cells owing to the use of combined anesthetic techniques; however, the reduction in opioids did not improve cancer outcomes.

Several retrospective database studies have suggested potentially different effects of opioids on different cancer subtypes [137,141]. Additionally, different opioids may have different effects on the immune system. For example, morphine and fentanyl suppress NK cell activity and lymphocyte proliferation, whereas oxycodone causes minimal immunosuppression [142]. A recent review highlighted the dose-dependent and short-lived nature of the immunosuppressive effects of opioids [143]. Therefore, currently, there is no basis for changing perioperative opioid prescriptions because of concerns about cancer progression.

NITROUS OXIDE

There are insufficient data for nitrous oxide. In a secondary analysis of a trial on colorectal cancer (n = 400), there was no difference in cancer recurrence or death between patients who received nitrous oxide or nitrogen during isoflurane/remifentanyl anesthesia and those who did not when followed for 4-8 years after surgery [144].

OTHER INTRAVENOUS AGENTS

Both ketamine and thiopental inhibited NK cell activity in animal models [31,145,146]. In an animal model, ketamine induced tumor metastasis more efficiently than other intravenous agents. Thiopental treatment also increased metastasis, whereas propofol treatment prevented metastasis [31]. Ketamine upregulates the levels of anti-apoptotic proteins in human breast cancer cell lines, which helps the cells invade and proliferate [147].

$\alpha 2$ ADRENOCEPTOR AGONISTS

Clonidine and dexmedetomidine are potent $\alpha 2$ -adrenoceptor agonists with analgesic, opioid-sparing, sedative, and anxiolytic effects. Therefore, they are widely used in general anesthesia and intensive care units. Clonidine, an older $\alpha 2$ -adrenoceptor agonist, is used as a part of multimodal analgesia in oral form. Compared with clonidine, dexmedetomidine, a more selective $\alpha 2$ adrenoceptor agonist, is administered intravenously and is much more effective with fewer side effects. As a sympatholytic agent, $\alpha 2$ -adrenoceptor agonist is theoretically an attractive option for general anesthesia in patients with cancer owing to its analgesic effects and reduction of catecholamines. In addition, some studies have found that dexmedetomidine is anti-inflammatory and reduces serum TNF- α , IL-6, PI3K, and AKT [148-150]. However, dexmedetomidine reduces both pro- and anti-inflammatory cytokines, but a greater reduction in anti-inflammatory cytokines (IL6/IL10 and IL8/IL1) by dexmedetomidine leads to a proinflammatory state [151].

Laboratory studies in murine models (lung, colon, and breast cancer) have shown a dose-dependent increase in tumor cell retention and metastasis following stimulation with $\alpha 2$ -adrenergic receptors [152]. Numerous *in vivo* and *in vitro* studies have shown that dexmedetomidine increases the risk of recurrence. Dexmedetomidine increased cancer cell survival through activation of HIF-1 α , upregulating the expression of survivin, metalloproteinases, and signal transducer and activator of transcription 3 (STAT3). These processes are related to cell migration and metastatic transition [15,18-21,62-64,76,149,153,154]. In addition, dexmedetomidine induces the proliferation of myeloid-derived suppressor cells, increases VEGF production, and promotes tumor metastasis [18].

A retrospective single-center study (n = 250) found that dexmedetomidine was associated with a decrease in overall

survival, but not in recurrence-free survival, in NSCLC [64]. Another retrospective study of nearly 650 patients (breast or lung cancer) found that patients who received low-dose clonidine during surgery had similar recurrence-free and overall survival rates to those who did not [155].

There is no high-quality evidence supporting the use of $\alpha 2$ -adrenoceptor agonists in patients with cancer. Prospective randomized controlled trials are needed to determine whether the effects observed in *in vitro* and *in vivo* studies can be observed in practice. However, given the potential harm caused by dexmedetomidine, avoiding its use when safe alternatives are available may be prudent. Several randomized been conducted, one of which is expected to be completed by 2024 for breast cancer surgery (NCT03109990) [156].

LOCAL ANESTHETICS

Local anesthetics are used for both systemic intravenous infusions and neuraxial and peripheral nerve blocks. Lidocaine is a short acting sodium channel blocker that acts to decrease nerve conduction [125,157-159]. Continuous lidocaine infusion is usually administered during anesthesia as a component of multimodal analgesia and as part of the enhanced recovery after surgery (ERAS) protocol to aid in the recovery of bowel movements and decrease opioid consumption.

In *in vitro* studies, systemic lidocaine has been shown to protect against cancer recurrence. Lidocaine has anti-inflammatory and antitumor effects through multiple pathways [160-164]. In addition to directly affecting cancer cells through the blockade of voltage-gated sodium channels in tumor cells, lidocaine reduced IL1, IL8, and TNF- α [165,166]. Lidocaine reduced cancer cell viability and migration in laboratory studies and improved the survival of 4T1 syngeneic breast cancer mice [167]. In that study, intravenous lidocaine reduced the number of pulmonary metastases when used in combination with volatile anesthesia, thus reducing the pro-cancer effects of volatile anesthesia in a mouse model [168]. In another mouse study, the addition of lidocaine to the chemotherapy drug cisplatin reduced the number of lung metastases compared with the control or cisplatin alone [86].

There are numerous suggested pathways responsible for the antitumor effects of lidocaine [86,169-174]. However, clinical data are limited. In a retrospective study of approximately 2,000 patients (pancreatic cancer), intravenous lido-

caine infusion was associated with a modest increase in 1- and 3-year overall survival (68% vs. 63% for 1-year overall survival and 34% vs. 27% for 3-year overall survival), with no difference in disease-free survival [172]. Another retrospective study on radical cystectomy for bladder cancer (n = 144) found that intraoperative lidocaine administration was associated with a reduction in overall mortality (adjusted HR, 0.36; 95% CI, 0.12–0.83) and cancer recurrence (30% vs. 47%) within 2 years compared to patients who did not receive lidocaine [175].

No studies have shown that lidocaine infusions have anti-cancer effects [159,160,171,176]. The upcoming VAPOR-C trial will investigate the effectiveness of lidocaine (lung and colorectal adenocarcinoma) in a 2×2 factorial design comparing propofol and sevoflurane general anesthesia with or without intravenous (IV) lidocaine (NCT04316013) [105].

To avoid overdose toxicity, IV lidocaine infusions have dose-limitation [159,160]. Most clinical studies have used a bolus of 1.5 mg/kg IV at induction, followed by 2 mg/kg/h IV infusion [172], or a bolus of 1 mg/kg IV, followed by 1.5 mg/kg/h IV infusion [175].

GLUCOCORTICOIDS

Glucocorticoids are widely used as adjuvant therapy in patients with metastatic cancer to prevent chemotherapy-induced nausea and vomiting and to reduce pain. Dexamethasone is commonly administered during anesthesia to prevent postoperative nausea and vomiting and for analgesia.

Glucocorticoids have anti-inflammatory effects that can help in cancer recurrence; however, they also have immunomodulatory effects that can impair cancer cell destruction.

However, the existing evidence is inconsistent. In preclinical studies, dexamethasone was associated with increased proliferation of some solid cancer cell lines but not others [177].

A retrospective study of patients who underwent cytoreductive surgeries for ovarian [178] and endometrial cancer [179] showed that cancer recurrence did not differ between patients who received dexamethasone (4–10 mg IV) during surgery and those who did not [178,179]. In another retrospective study of NSCLC, intraoperative administration of dexamethasone was associated with prolonged postoperative survival [180]. In contrast, a retrospective study of nearly 500 patients with rectal cancer found that the administration of dexamethasone during surgery was associated with reduced disease-free survival [181].

Therefore, there is insufficient evidence to suggest that practices should be changed based on concerns regarding cancer recurrence.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Several retrospective studies have shown that intraoperative administration of non-steroidal anti-inflammatory drugs (NSAIDs) reduces cancer recurrence and improves survival. A single-center retrospective study (n = 720 patients with breast cancer) found that intraoperative administration of ketorolac or diclofenac was associated with prolonged disease-free and overall survival [182]. Another retrospective study (n = 327 patients with breast cancer) found that patients who received ketorolac during surgery had a lower rate of cancer recurrence than in those who received sufentanil, ketamine, or clonidine [183]. Yeh et al. [184] conducted a nationwide cohort study (n = 15,574 patients with hepatocellular carcinoma) that revealed an association between perioperative administration of NSAIDs and a reduced risk of cancer recurrence (HR, 0.81; 95% CI, 0.73–0.90; P < 0.001).

In a small prospective study (n = 38 patients with breast cancer), patients randomly received propranolol and etodolac or placebo for 5 days before and after surgery [185]. Those receiving propranolol and etodolac showed reduced levels of cancer recurrence markers [185].

Regarding anticancer mechanisms, NSAIDs may play a significant role by inhibiting a pro-inflammatory tumor microenvironment by downregulating VEGF and reducing regulatory T cell infiltration. This leads to a decrease in angiogenesis and lymphangiogenesis, which are critical processes for tumor growth and spread. Additionally, NSAIDs have been shown to reduce NK cell suppression and metastasis in mouse models, further hindering cancer progression. Together, these mechanisms underscore the potential of NSAIDs in preventing cancer recurrence by targeting various aspects of tumor biology and immune response [39].

CONCLUSION

In this review, I briefly discuss cancer cell biology and the interaction between residual tumor cells, growth and migration factors, and the host immune system, in relation to the effects of commonly used anesthetics and adjuvants. The currently available data are insufficient to form a definitive

recommendation for the choice of anesthetics despite the numerous studies that have been published.

The apparent protumor or antitumor effect shown in *in vitro* or *in vivo* studies was not clear in clinical settings. Therefore, this process appears to be much more complex than we initially believed, probably owing to the heterogeneous biology of different malignancies and surgeries, as well as patient populations.

Several multicenter, randomized controlled clinical trials are currently underway to shed light on this topic. Given the current state of evidence, the clinical impact of anesthetics and adjuvants on cancer recurrence and metastasis should be investigated by conducting high-quality randomized studies.

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CONFLICTS OF INTEREST

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

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