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REVIEW

The Role of Inhaled Anesthetics in Tumorigenesis and Tumor Immunity

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Abstract: Inhaled anesthetics are widely used for induction and maintenance of anesthesia during surgery, including isoflurane, sevoflurane, desflurane, haloflurane, nitrous oxide (N_2O), enflurane and xenon. Nowadays, it is controversial whether inhaled anesthetics may influence the tumor progression, which urges us to describe the roles of different inhaled anesthetics in human cancers. In the review, the relationships among the diverse inhaled anesthetics and patient outcomes, immune response and cancer cell biology were discussed. Moreover, the mechanisms of various inhaled anesthetics in the promotion or inhibition of carcinogenesis were also reviewed. In summary, we concluded that several inhaled anesthetics have different immune functions, clinical outcomes and cancer cell biology, which could contribute to opening new avenues for selecting suitable inhaled anesthetics in cancer surgery.

Keywords: inhaled anesthetics, cancer, tumorigenesis, surgery, immune

Introduction

In the twenty-first century, cancer has been expected to rank as the second leading cause of death in the United States,[1] and is the most vital obstacle to extending life expectancy in every country of the world.[2] In the majority of solid cancers, surgery resection under anesthesia remains the principal treatment strategy. However, it was controversial whether general anesthetics, especially inhalational anesthetics, may induce growth, migration and invasion of cancer cells. Although guidelines for surgical procedures have been developed for different types of cancers, there is currently no guidelines of anesthesia selection during surgery for cancer patients.[3]

Inhaled anesthetics, often widely used for induction and maintenance of anesthesia during surgery, include isoflurane, sevoflurane, desflurane, haloflurane, nitrous oxide (N_2O), enflurane and xenon. Some studies showed that inhaled anesthetics such as sevoflurane and isoflurane inhibit immune response and play a pivotal role in the tumorigenesis, which may be unfavorable for cancer patient outcomes.[4] Nevertheless, some studies found that inhaled anesthetics did not affect the survival of cancer patients.[5,6] Hence, the key issue of whether inhaled anesthetics influence the cancer progression remains unclear. However, the impacts of choosing different inhaled anesthetics on tumor immune response, cancer cell biology, and the prognosis of cancer patients should be carefully considered.

Therefore, this review aims to explore the role of various types of inhaled anesthetics in cancer development and immune response to guide us to select inhaled anesthetics during cancer surgery.

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Sevoflurane and Cancer

The Effect of Sevoflurane on Clinical Outcomes and Immune Function of Cancer Patients

Sevoflurane is a widely used inhaled anesthetic to maintain intraoperative anesthesia during cancer surgery.[7] Numerous retrospective analysis investigations have shown that cancer patients anaesthetized with sevoflurane had worse clinical outcomes than those received anesthesia with propofol in the surgery for breast, colon, rectal and gastric cancers.[8,9] Furthermore, compared with the propofol group, the sevoflurane group displayed a higher rate of cancer recurrence in breast cancer patients undergoing modified radical mastectomy,[10] and increased the risk of death in patients with high-grade glioma undergoing tumor resection.[11] But recently, a randomized control trial involved in more than 2000 women who underwent breast cancer surgery demonstrated that there was no significant difference in breast cancer recurrence rate among women receiving general anesthesia (sevoflurane and opioids) and regional anesthesia analgesia (paravertebral block and propofol).[12] Therefore, according to published reports, compared with propofol, sevoflurane might have no effect on the prognosis of breast cancer patients during the surgery, but it could have an unfavorable effect on the outcomes of patients with other cancers, which need further investigation.

As for immune response, it has been observed that inhaled anesthesia during surgery may induce immune response. For example, the counts of CD3+ cells, CD4+ cells, natural killer (NK) cells, and the CD4+/CD8+ ratios in the blood samples were significantly lower in the sevoflurane group than that of propofol group among the patients undergoing laparoscopic radical hysterectomy for cervical cancer.[13] An in vitro study illustrated that sevoflurane reduced NK cell-mediated cytotoxicity partly via inhibition of adhesion molecule leukocyte function-associated antigen-1 (LFA-1).[14] Furthermore, compared with propofol anesthesia with postoperative ketorolac analgesia group, sevoflurane anesthesia with postoperative fentanyl analgesia group exerted a more significantly unfavorable effect on the immune function by deteriorating NK cell cytotoxicity in patients undergoing breast cancer surgery, indicating that avoiding the use of sevoflurane could reduce immune suppression in surgery.[15] One group used serum from patients undergoing primary breast cancer surgery who received sevoflurane anesthesia with opioid analgesia to be cocultured with healthy human donor NK cells and found that it reduced NK marker expression or secretion of cytokines such as NK cell activating receptor CD16, interleukin-10 (IL-10) and IL-1β.[16] These studies suggest that sevoflurane could inhibit immune response by regulating the expression of cytokines and decreasing NK cell cytotoxicity.

The Biological Function of Sevoflurane in Promoting Oncogenesis

Several studies have found that sevoflurane induced cell proliferation in various cancers. Our previous study observed that after exposure with sevoflurane, human cervical cancer cells showed increased cell proliferation ability and decreased cell apoptosis in comparison with the corresponding untreated cancer cells.[17] Consistently, an experimental study showed that sevoflurane increased cell proliferation in both estrogen receptor-positive (ER-positive) and ER-negative breast cells.[18] The treatment with serum from patients undergoing sevoflurane anesthesia with opioid analgesia for breast carcinoma surgery promoted the proliferation of breast cancer cells in comparison with those patients receiving propofol/paravertebral anesthesia group.[19] Another study reported that postoperative serum from breast cancer surgery patients given sevoflurane anesthesia with opioid analgesia cocultured with ER-negative breast cells reduced cancer cell apoptosis compared with serum from patients given propofol-paravertebral anesthesia.[20] This phenomenon indicated that anaesthetics might promote cancer progression by affecting the serum environment and reducing cancer cells' apoptosis.[20] In addition, it was uncovered that sevoflurane enhanced proliferation of human hepatocellular carcinoma (HCC) cells under conditions of high glucose and high insulin, implying that sevoflurane promoted cell growth under a physiological condition that mimicked diabetes during surgery.[21] Mechanically, Shi et al[22] revealed that sevoflurane induced the self-renewal and proliferation of glioma stem cells in vitro through regulation of hypoxia-inducible factor (HIF) pathway, suggesting that sevoflurane might enhance tumor growth by inducing proliferation of cancer stem cells to impact the prognosis of cancer patients. In neck squamous cell carcinoma cells, the expression of pro-oncogenic protein markers such as HIF-2α and nuclear p-p38 was increased under exposure to sevoflurane in postanesthesia compared with that in preanesthesia, indicating that sevoflurane may play a pivotal role in unfavorable outcomes of cancer treatment.[23]

It has been found that sevoflurane induced cell migration and invasion ability via upregulating CD44 expression in human glioblastoma cells compared with the corresponding

untreated cells.[24] Similarly, sevoflurane exerted a stimulative effect on the migration of human cervical cancer cells in our previous study.[17] In addition, another study uncovered that upregulated transforming growth factor-beta (TGF-β) and osteopontin signaling pathways played pivotal roles in sevoflurane-mediated renal cell carcinoma (RCC) metastasis potential.[25] In an in vivo study, one group revealed that sevoflurane increased tumor volume and invasion/migration distance in nude mice compared with the group without sevoflurane[24] (Table 1, Figure 1).

The Biological Function of Sevoflurane in Suppressing Oncogenesis

Contrary to the carcinogenic properties of sevoflurane, studies have demonstrated that sevoflurane anesthesia induced p53-dependent apoptosis in human colon cancer cell.[26] In head and neck squamous cell cancer (HNSCC), sevoflurane inhibited cell proliferation and induced cell apoptosis via the downregulation of p-Akt and B-cell lymphoma-2 (Bcl-2) protein expression, and upregulation of Fas/FasL signal pathway.[27] Similarly, one group found that human lung adenocarcinoma cells treated with sevoflurane had significant proliferation inhibition and apoptosis induction, with the downregulation of the expressions of X-linked inhibitor of apoptosis protein (XIAP) and survivin protein, and upregulation of activated caspase-3 expression.[28] In line with this, another group showed that sevoflurane combined with cisplatin led to a greater extent suppression of human lung adenocarcinoma cells' growth in comparison with sevoflurane or cisplatin alone, which might also be related to the downregulation of XIAP and survivin protein.[29] Notably, microRNA (miRNA)-203 was upregulated by sevoflurane and mediated the function of sevoflurane in

Table 1 The Biological Function of Sevoflurane in Cancer

Anesthetics	The Role of Anesthetics in Oncogenesis	Downstream Gene Regulated by Anesthetics	Function	References
Sevoflurane	Promotes oncogenesis	Induces HIF pathway	Promote glioma stem cells proliferation	[22]
		Upregulates CD44	Promotes glioblastoma cell migration and invasion	[24]
		Upregulates TGF-β and osteopontin	Induces RCC cells metastasis	[25]
	Suppresses oncogenesis	Downregulates p-Akt and Bcl-2	Inhibits neck squamous cell cancer cell proliferation	[27]
		Upregulates Fas/FasL	Induces HNSCC cells apoptosis	[27]
		Downregulates XIAP, survivin and upregulates caspase-3	Inhibits proliferation and induce apoptosis	[28]
		Upregulates miRNA-203	Inhibits breast cancer cells proliferation	[30]
		Downregulates MMP-2, MMP-9, fascin, and ezrin	Inhibits the invasion and migration of human lung cancer cells	[31]
		Downregulates MMP-2	Inhibits migration of glioma cells	[32]
		Downregulates HIF-1α	Inhibits hypoxia-induced growth and metastasis of lung cancer cells	[33]
		Upregulates miR-637 and downregulates Akt1	Suppresses glioma cells migration and invasion	[35]
		Upregulates miR-34a/ADAM10 axis	Suppresses the migration and invasion of colorectal cancer cells	[36]
		Inhibits ERK signaling pathway	Suppresses colon cancer cells proliferation, invasion and epithelial-mesenchymal transition, induces apoptosis and autophagy	[7]
		Inhibits Ras and RhoA GTPase	Suppresses cervical cancer cells migration	[37]
		Inactivates PI3K/AKT pathway	Suppresses osteosarcoma cells metastasis	[38]

Abbreviations: TGF-β, transforming growth factor-beta; RCC, renal cell carcinoma; p-Akt, phosphorylated AKT; Bcl-2, B-cell lymphoma-2; Fas, a cell surface receptor can activate apoptosis by binding to its ligand; XIAP, X-linked inhibitor of apoptosis protein; ADAM10, a disintegrin and metalloprotease-10; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide 3-kinase.

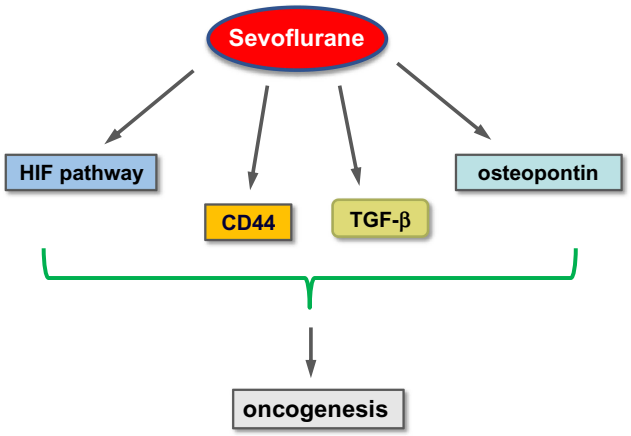

Figure 1 Sevoflurane exerts oncogenic effect by targeting multiple downstream molecules in human cancer.

proliferation inhibition of breast cancer cells, implying that miR-203 could be a potential target for the treatment of breast cancer patients with sevoflurane.[30] A recent research noted that the proliferation was inhibited but apoptosis and autophagy were induced by the treatment with sevoflurane in colon cancer cells via inhibition of the ERK signaling pathway in vivo and in vitro.[7] One study revealed that sevoflurane inhibited the invasion and migration of human lung cancer cells by downregulating the expression of the matrix metalloproteinases-2 (MMP-2), MMP-9, fascin, and ezrin proteins.[31] One study demonstrated that sevoflurane combined with cisplatin reduced the invasion inhibitory synergy that was associated with the downregulation of MMP-2 and MMP-9 in lung cancer.[29] Additionally, another group elucidated that sevoflurane played an inhibitory role on the migration and suppressed MMP2 activity in glioma cells.[32] Similarly, sevoflurane inhibited hypoxia-induced growth and metastasis by suppressing HIF-1α and its downstream gene expressions in lung cancer.[33] Furthermore, sevoflurane was able to attenuate platelets-induced invasion of lung cancer cells by downregulating platelets' activity, which indicates that regulation of platelets' activity by sevoflurane could be an attractive novel approach to fight against tumor cell metastasis during cancer surgery.[34] It has been shown that sevoflurane suppressed glioma cell migration and invasion by upregulation of miR-637 expression and thereby inhibited the activity of Akt1 in a dose-dependent manner.[35] A recent study also found that sevoflurane suppressed the migration and invasion by activating miR-34a/a disintegrin and metalloprotease-10 (ADAM10) axis in colorectal cancer cells.[36] One group uncovered that sevoflurane suppressed invasion and epithelial-mesenchymal transition by inactivating the ERK signaling pathway in colon malignant cancer cells.[7] It has been found that sevoflurane obviously reduced migration in cervical cancer by suppression of Ras and RhoA GTPase activities.[37] Consistently, it has been revealed that sevoflurane played a key role in the inhibition of cell metastasis on osteosarcoma cells via inactivating the PI3K/AKT pathway.[38] These adverse effects indicated that sevoflurane has different cell biological effects on various cancer types (Table 1, Figure 2).

Isoflurane and Cancer

The Impact of Isoflurane on Clinical Outcomes and Immune Function of Cancer Patients

Isoflurane is a volatile general anesthetic that can be used to induce and maintain general anesthesia to eliminate behavioral response in patients undergoing tumor resection.[39] A survival investigation indicated that the use of isoflurane or desflurane alone during glioblastoma surgery did not affect overall survival (OS) or progression-free survival (PFS) at 1 or 5 years.[5] Postoperatively, the plasma levels of IL-6 and IL-10 in 35 patients with colorectal cancer after surgery treated with isoflurane were significantly higher than baseline values before surgery.[40] Contrary to the above phenomena, at post-operatively, the percentage of CD4-positive and CD28-positive T-helper cells, and the ratio of IL-4 in the blood samples of 30 lung cancer patients treated with isoflurane did not change compared with before surgery.[41]

The Biological Function of Isoflurane in Promoting Oncogenesis

Isoflurane enhanced the malignant activity of cancer cells such as proliferation and chemo-resistance through upregulating the expression of HIF-1α and its downstream genes in prostate

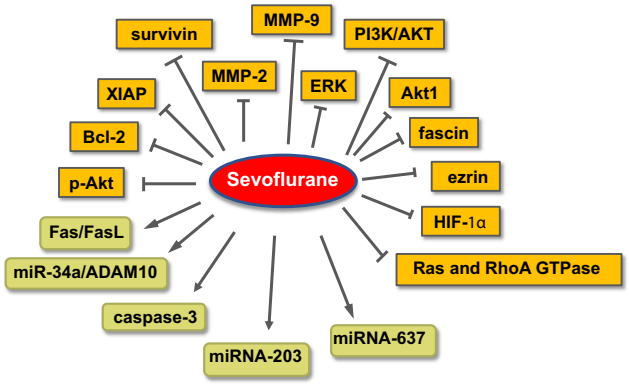

Figure 2 Sevoflurane exerts tumor inhibitive effect by regulating several downstream molecules in human cancer.

cancer.[42] Notably, propofol attenuated cancer cell malignant ability in part by suppression of isoflurane-triggered HIF-1α activation.[42] In glioblastoma cells, exposure to isoflurane promoted cancer cell proliferation and inhibited apoptosis.[43] Biologically, isoflurane led to triggering cell growth and malignant potential by activating the HIF signaling pathway in human renal cancer cells.[44] Isoflurane increased the proliferation of non-small cell lung cancer (NSCLC) cells by activating the Akt-mTOR signaling pathway. Consistently, isoflurane exposure generated an inhibitory effect on apoptosis via upregulating Caveolin-1 expression in human colon cancer cell.[45] In the mouse model experiment, it was found that under exposure with isoflurane, melanoma grew faster in male mice than those without treatment with isoflurane, but not in female mice, indicating that the gender of species should be carefully considered when isoflurane was studied for tumor growth.[46]

Under treatment with isoflurane, the migration ability of ovarian cancer cells was obviously increased by promoting expression of MMP-2 and MMP-9,[47] and induction of angiogenetic markers VEGF and angiopoietin-1 protein expression to enhance angiogenesis, whereas these effects were abolished by blocking the IGF-1R signaling.[47] Moreover, isoflurane increased NSCLC cell migration and invasion by activating the Akt-mTOR signaling pathway.[48] In line with these, isoflurane enhanced cancer cell migration through upregulating the expression of HIF-1α and its downstream genes in prostate cancer[42] (Table 2, Figure 3).

The Biological Function of Isoflurane in Suppressing Oncogenesis

Isoflurane inhibited cell proliferation and reduced cell viability in HCC.[39] Furthermore, migration and invasion abilities of liver cancer cells were inhibited by isoflurane by attenuating nuclear factor-kappaB (NF-κB) activity.[39] These results uncovered that isoflurane plays an inhibitory role in liver oncogenesis (Table 2, Figure 3). In summary, these phenomena suggest that treatment with isoflurane might be a promoting factor in the progression of most types of cancers.

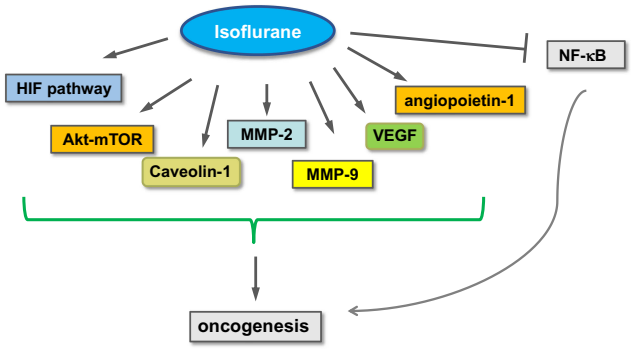

Figure 3 Isoflurane plays oncogenic or tumor inhibitive roles by modulating downstream molecules in human cancer.

Desflurane and Cancer

The Impact of Desflurane on Immune Function and Clinical Outcomes of Cancer Patients

The anesthetic gas desflurane was first applied for clinical practice in 1992. Due to its low solubility, desflurane can be eliminated more quickly and consequently be awaken more easily.[49] For colon cancer surgery, patients treated with desflurane anesthesia were associated with a higher mortality rate (43.5% versus 13.4%), a higher local recurrence (9.1%

Table 2 The Biological Function of Isoflurane in Cancer

Anesthetics	The Role of Anesthetics in Oncogenesis	Downstream Gene Regulated by Anesthetics	Function	References
Isoflurane	Promotes oncogenesis	Upregulates HIF pathway	Promotes prostate cancer and RCC cells proliferation, migration and chemoresistance	[42,44]
		Activates Akt-mTOR pathway	Promotes NSCLC cells proliferation, migration and invasion	[48]
		Upregulates Caveolin-1	Induces colon cancer cell apoptosis	[45]
		Upregulates MMP-2 and MMP-9, VEGF and angiopoietin-1	Promotes ovarian cancer cells migration and angiogenesis	[47]
	Suppress oncogenesis	Downregulates NF-κB	Inhibits liver cancer cells migration and invasion	[39]

Abbreviations: HIF, hypoxia-inducible factor; RCC, renal cell carcinoma; Akt, protein kinase B; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; MMP, matrix metalloproteinase; NF-κB, nuclear factor-kappaB.

versus 5.8%), and increased postoperative metastasis rate (43.5% versus 13.4%) than propofol anesthesia group regardless of tumor node metastasis (TNM) stages during the 10 years' follow-up.[50] Similarly, a retrospective cohort study uncovered that patients in desflurane anesthesia group had a worse outcome, such as higher mortality rate (75.0% versus 30.8%), distant metastasis (15.9% versus 5.5%) or a higher local recurrence (70.1% versus 37.8%), compared with propofol group in HCC patients who underwent hepatectomy during 10 years' follow-up.[51] In contrast, a clinical research found that epithelial ovarian cancer patients at stage III who were given desflurane were related to a less overall rate of recurrence during primary cytoreductive surgery compared with patients who were given sevoflurane.[52] But the Kaplan–Meier curves demonstrated that PFS and OS rates at 1 and 5 years were similar for patients given desflurane in comparison with isoflurane during the glioblastoma surgery.[5] When it comes to immune response, desflurane exerted a favorable effect on immune response in breast cancer patients because of preservation of IL-2/IL-4 and CD4(+)/CD8(+) T cell ratio in the perioperative period.[53]

The Biological Function of Desflurane in Promoting Oncogenesis

An in vitro experiment noted that the expression of metastatic-related genes such as VEGF-A, MMP-11, CXC chemokine receptor 2 (CXCR2) and TGF-β was increased after human ovarian cancer cells were exposed to desflurane at a concentration of 10.3% for 2h, which promoted ovarian cancer cell migration[54] (Table 3).

The Biological Function of Desflurane in Suppressing Oncogenesis

One study found that volatile anesthetics desflurane attenuated the migration and invasion ability of colorectal cancer cells in vitro by downregulating the expression of MMP-9.[55] As for desflurane, it played a pivotal role in leading to adverse outcomes in most patients undergoing cancer surgery whereas further exploration of specific biological mechanism is still to be required (Table 3).

Halothane and Cancer

It was revealed that the survival rates of patients treated with halothane from the third year to the seventh year were higher than patients who were anesthetized with ether in breast cancer surgery.[56] In lung cancer patients, for five year follow-up, the results showed that the survival rates of halothane-anesthetized patients had surpassed that receiving treatment with ether group.[57]

In an in vitro experiment, a research team revealed that the antitumor activity of IFN-γ was enhanced when cotreated colon cancer cells with IFN-γ and halothane compared with non-halothane treatment, suggesting that halothane enhanced the antitumor activities of IFN-γ against human colon cancer cell.[58] Conversely, comparing the two groups of treatments with or without halothane, halothane reduced the adhesion effect of tumor cell and promoted the metastasis of melanoma cell by downregulation of intercellular adhesion molecule-1 expression.[59]

Other Inhaled Anesthetics and Cancer

N_2O and Cancer

N_2O inhibited leukemia cell growth and induced cell apoptosis by attenuating the activity of vitamin B12 and the production of methionine synthase.[60] In line with that, when ovarian cancer cells were exposed to N_2O, it showed a tendency toward a decreased cell growth but existed no significant difference.[61]

Enflurane and Cancer

Comparison of the three different methods of anesthesia with halothane group, enflurane and isoflurane anesthesia group, local anesthesia and neuroleptanalgesia group, it has been found that the types of anesthesia did not affect

Table 3 The Biological Function of Desflurane in Cancer

Anesthetics	The Role of Anesthetics in Oncogenesis	Downstream Gene Regulated by Anesthetics	Function	References
Desflurane	Promotes oncogenesis	Upregulates VEGF-A, MMP-11, CXCR2 and TGF-β	Promotes ovarian cancer cell migration	[54]
	Suppresses oncogenesis	Downregulates MMP-9	Inhibits colorectal cancer cells migration and invasion	[55]

Abbreviations: VEGF-A, vascular endothelial growth factor-A; MMP, matrix metalloproteinase; CXCR2, CXC chemokine receptor 2; TGF-β, transforming growth factor-beta.

the 5-years survival rates of localized cutaneous melanoma patients for melanoma excision.[6]

Xenon and Cancer

Xenon inhibited the migration of both ER-positive and ER-negative breast cancer cells and also reduced the release of the angiogenesis cytokine regulated on activation, normal T-cell expressed, and secreted (RANTES).[62] Hence, the impacts of these anesthetics on tumorigenesis are limited and indefinite.

Conclusion

In conclusion, the effect of sevoflurane on the outcomes of cancer patients needs further investigation. Remarkably, sevoflurane inhibited immune response by regulating the expression of cytokines and decreasing NK cell cytotoxicity. However, studies also indicated that sevoflurane may have diverse effects on cell biology for different tumor types. Due to limited literature on the effects of isoflurane on immune function and clinical outcomes during cancer surgery, the role of isoflurane remains uncertain. Additionally, isoflurane effectively affected several bioprocesses in the progression of mostly cancer, such as cancer cell proliferation, metastasis, chemo-resistance and angiogenesis. As for desflurane, it played a pivotal role in adverse outcomes in most cancer patients undergoing surgery, whereas further exploration of the specific mechanisms is needed. Finally, for other inhaled anesthetics mentioned in this review, such as halothane, N_2O, enflurane and xenon, their impacts on tumor development and progression have been little studied. Hence, further experimental researches and prospective clinical studies are needed to provide more specific information in order to determine the impact of anesthesia on postoperative cancer outcomes and to offer guidance for the selection of anesthetics during cancer surgery.

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Author Contributions

All authors contributed to the conceptualization of this review, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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