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REVIEW

Effects of Anesthesia and Anesthetic Techniques on Metastasis of Lung Cancers: A Narrative Review

Zhenghuan Song
Jing Tan

Department of Anesthesiology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, People's Republic of China

Purpose: Tumor recurrence and metastasis are essential for the mortality and morbidity of cancer. Surgical resection of solid tumors is the conventional treatment approach for malignant tumors. However, even after undergoing radical surgery, certain patients develop local or distant metastasis, which may contribute to treatment failure. Anesthesia and anesthetic techniques are widely used in the perioperative period. Emerging evidence indicates that anesthetics influence tumor recurrence and metastasis. Therefore, the current review summarizes the effects of anesthesia and anesthetic techniques on tumor recurrence and lung metastasis.

Methods: Relevant literature was retrieved from the following databases: Medline/PubMed, CNKI and Wanfang. A total of 109 articles were selected and analyzed in this research.

Results: (1) A variety of intravenous anesthetics may affect metastasis or tumor growth, though the evidence is contradictory and inconsistent, and the clinical data are still inconclusive. (2) Volatile anesthetics have proinflammatory effects and may have direct and indirect effects on the survival of cancer cells. (3) Although the relevant clinical data are limited, there is strong evidence in vitro that local anesthetics have a protective effect on cancer recurrence. (4) No mode of anesthesia has been determined to be beneficial to patients with cancer, but clinical studies are currently recommended for anesthesia modality and composite use.

Conclusion: Available data suggest that anesthesia and anesthetic techniques might play an important role in tumor progression and lung metastasis, the understanding of which will help in designing more effective management of the tumor and attaining fewer side effects.

Keywords: anesthesia, anesthetics, tumor, recurrence, lung metastasis

Introduction

Malignant cancer is a leading cause of mortality worldwide. The majority of deaths result from distant tumor metastasis.[1,2] It is expected that there will be 28.4 million new cases of cancer in 2040.[3] Surgical resection is the main effective option for early-stage cancer at present.[4] Approximately 56–91% of patients with lung, breast, bladder, and colorectal cancer will undergo surgery.[5] However, surgery is one of the most important factors affecting cancer progression and metastases formation, and the process of tumor manipulation might result in increased tumor cells being released into the vasculature and the promotion of metastasis.[6] Despite advances in medical techniques (eg, radiation therapy, chemotherapy, targeted therapy and other new strategies) leading to remarkable progress in the treatment of cancer,

Correspondence: Jing Tan
Department of Anesthesiology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University, 42 Baiziting, Xuanwu Section, Nanjing, Jiangsu Province, People's Republic of China
Tel +86-02583284765
Email tanjing@njmu.edu.cn

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tumor metastasis is a major challenge of cancer therapy, and the lungs are the most frequently identified site of systemic metastases.[7,8] Anesthesia management is a crucial part of the surgical process. Current research has revealed that modern anesthesia not only has a good anesthetic effect but also potentially influences the interactions between tumor cells, including the immune system and tumor microenvironment.[9–12] For example, volatile anesthetics and opioids can suppress cell-mediated immunity and promote cancer cell proliferation.[13,14] Thiopental and ketamine have been implicated in increasing lung retention and lung metastasis of tumor cells via diminished natural killer cell function.[12] Therefore, understanding the molecular mechanism underlying these effects is critically important to help guide treatment choices by anesthetists.

In this review, we aim to provide additional, valuable information regarding the role of anesthesia and anesthetic techniques in different aspects of lung tumor metastasis and recurrence.

Search Strategy

Electronic databases were searched until September 2021 using a string of medical subject heading terms or related terms. The primary keywords used in the searches were as follows: "anesthesia and metastases", "lung tumor", "anesthetic agents and cancer", "inhalation anesthesia and cancer", "cancer recurrence" and "anesthetic technique and cancer". PubMed was used as a search engine for the Medline database and as the main source of information for this paper. Furthermore, the China National Knowledge Infrastructure (CNKI) and Wanfang Database were also searched for relevant articles. The language was restricted to English and Chinese. The article type included review articles, cell animal experiments, observational studies and clinical trials. In addition, we searched related articles in the reference lists of the included articles. A total of 109 articles were selected and analyzed in this research. Then, two authors reviewed these retrieved articles for suitability.

Anesthetics Promote Lung Metastasis and Tumor Recurrence

Anesthetics are a heterogeneous group of drugs with multiple functions and mechanisms of action. Previous studies have reported that the choice of anesthetics can affect the prognosis of patients undergoing cancer surgery. The following section summarizes common anesthetics and their effects.

Intravenous Anesthetics

Intravenous anesthetics are widely used for general anesthesia, and they primarily target the central nervous system, including sedation, analgesia and muscle relaxants. Recent studies report that intravenous anesthesia affects tumor recurrence and metastasis through complex mechanisms.

Propofol

Propofol (2,6-diisopropylphenol) is commonly used for the induction and maintenance of general anesthesia. It is characterized by rapid induction and quick recovery. Studies report that propofol plays a role in cancer progression by modulating the expression of multiple signaling pathways; thus, studies have been conducted to explore the potential mechanisms.[15] In addition, preclinical and clinical studies have been conducted to explore the role of propofol in cancer progression (selected studies are summarized in Table 1).

In vivo Studies

Mice administered propofol anesthesia presented with less lung metastasis after primary tumor resection than mice administered sevoflurane.[16] Findings from nude mouse model studies show that propofol inhibits the growth of syngeneic 4T1 and human MDA-MB-231 breast cancer xenografts.[15,17] In addition, propofol downregulates the expression of E-cadherin and β-catenin in metastatic tumor tissues and inhibits lung metastasis of MADB106 tumor cells.[18,19]

In vitro Studies

Propofol inhibits the proliferation, migration and invasion of cancer cells and promotes apoptosis by regulating several signaling pathways and the expression of noncoding RNAs in vitro. For example, propofol inhibits the invasion and metastasis of lung cancer by downregulating the expression of matrix metalloproteinase (MMP)-2 and MMP-9.[20] Moreover, propofol inhibits the proliferation and metastasis of lung cancer H460 cells by inducing endoplasmic reticulum stress and the JNK signaling pathway.[21] Propofol downregulates p38MAPK signal transduction to inhibit cancer cell migration and invasion.[22] In addition, propofol upregulates the expression of apoptosis-related proteins by modulating the activities of miRNAs. For instance, propofol

Table 1 Effects of Propofol on Lung Metastasis of Tumor Cells

Title	Author	Year	Type	Significant Result
Effects of propofol on pulmonary metastasis of intravenous injected tumor cells and expressions of MTA1 and Wnt1 in rats.[19]	Zhang Yet al	2014	In vivo study	Propofol could inhibit pulmonary metastasis of intravenous tumor cells in a dose-dependent manner and down-regulate the expression of MTA1 and Wnt1 in metastatic tumor tissues.
Effects of propofol on pulmonary metastasis of intravenously injected MADB106 tumor cells and expression of E-cadherin and β-catenin in rats.[18]	Wang W et al	2015	In vivo study	Propofol can down-regulate the expression of E-cadherin and β-catenin in metastatic tumor tissues by inhibiting Wnt/ β-catenin pathway, and inhibit lung metastasis of intravenous MADB106 tumor cells in a dose-dependent manner.
Distinct effects of general anesthetics on lung metastasis mediated by IL-6/JAK/STAT3 pathway in mouse models.[17]	Li R et al	2020	In vivo study	In syngeneic mouse 4T1 and human MDA-MB231 breast cancer xenograft model, surgical resection of primary tumor in mice under sevoflurane anesthesia resulted in more lung metastasis than propofol.
Suppression of cell invasion and migration by propofol are involved in down-regulatin matrix metalloproteinase-2 and p38 MAPK signaling in A549 human lung adenocarcinoma epithelial Cells.[22]	Wu KC et al	2012	In vitro study	Propofol has a variety of anti-metastatic activities in A549 cells and can inhibit the migration and invasion of A549 cells. The possible signal pathway may be that it inhibits MMP-2 and MMP-9 and stimulates TIMP1 and TIMP2 by blocking the expression of MMP-2 and-9mRNA.
Propofol Inhibits Lung Cancer A549 Cell Growth and Epithelial-Mesenchymal Transition Process by Upregulation of MicroRNA-1284.[24]	Liu WZ et al	2018	In vitro study	Propofol could inhibit cell viability, migration, invasion, and the EMT process in lung cancer cells by regulation of miR-1284.
Propofol suppresses growth, migration and invasion of A549 cells by down-regulation of miR-372.[25]	Sun H et al	2018	In vitro study	Propofol inhibits the growth, migration and invasion of lung cancer A549 cells by down-regulating miR372 and inactivating Wnt/ β-catenin and mTOR pathways.
Propofol induces apoptosis of non-small cell lung cancer cells via ERK1/2-dependent upregulation of PUMA.[26]	Xing SG et al	2018	In vitro study	Propofol inhibits the survival and induces apoptosis of A549 cells in a dose-dependent manner in vitro. The mechanism may be that propofol inhibits cell survival and induces apoptosis through ERK1/2-dependent PUMA signaling pathway.
Propofol suppresses invasion of human lung cancer A549 cells by down-regulating aquaporin-3 and matrix metalloproteinase-9.[20]	Ye HJ et al	2016	In vitro study	Treatment with 50 and 100 μmol/L propofol for 24h significantly inhibits the number of invading cells by down-regulating the expression of AQP-3 and MMP-9 in A549 cells.
Propofol inhibits lung cancer cell viability and induces cell apoptosis by upregulating microRNA-486 expression.[30]	Yang N et al	2017	In vitro study	Propofol increased the level of miR-486 in H1299 and H1792 cells in a dose-dependent manner. Propofol decreased the cell survival rate, but increased the percentage of apoptotic cells and the protein expression of FOXO1, FOXO3, Bim, pre-caspases and activated caspases.
Propofol suppresses LPS-induced nuclear accumulation of HIF-1alpha and tumor aggressiveness in non-small cell lung cancer.[23]	Yang N et al	2017	In vitro study	Inflammation stimulated by endotoxin enhances the function of HIF-1α by increasing the expression level, protein stability and nuclear localization of NSCLC cells, which leads to the increase of markers and mediators of migration and invasion. Propofol inhibited all these effects by inhibiting hypoxia inducible factor-1α.

(*Continued*)

Table 1 (Continued).

Title	Author	Year	Type	Significant Result
Propofol induces endoplasmic reticulum (ER) stress and apoptosis in lung cancer cell H460.[21]	Cui WY et al	2014	In vitro and in vivo	Propofol inhibits proliferation and induces apoptosis in H460 cells and inhibits tumor growth in vivo. propofol acts as a positive regulator in ER stress and JNK signaling pathway.
Impact of anesthetic agents on overall and recurrence-free survival in patients undergoing esophageal cancer surgery.[31]	Jun I.J et al	2017	Clinical study	Intravenous anesthesia with propofol (TIVA)was associated with better postoperative survival rates.

induces apoptosis of lung cancer cells by upregulating the expression of miRNA-486, FOXO1 and FOXO3 (fork box, O1 and 3), BIM (Bcl-2 cell death interaction mediator) and caspase-3.[23] Furthermore, it downregulates the expression of miR-372 to promote apoptosis of the lung cancer cell line A549. In addition, the expression of miR-1284 in lung cancer cells and A549 cells was significantly upregulated when the cells were cocultured with therapeutic concentrations of propofol, thus inhibiting the migration, invasion and epithelial-mesenchymal transformation of A549 tumor cells.[23–25] Moreover, propofol inhibits the survival and induces the apoptosis of A549 cells through the extracellular regulated protein kinase (ERK)1/2-dependent PUMA signaling pathway.[26]

Tumor hypoxia is a characteristic feature of the tumor microenvironment and promotes metastasis of several cancer types. Analysis of clinical samples showed that hypoxia inducible factor-1α (HIF-1α) is abnormally expressed in non-small-cell lung cancer (NSCLC).[27–29] Increased expression of HIF-1α is correlated with poor prognosis. Propofol significantly decreases HIF-1α and ROS levels induced by lipopolysaccharide (LPS) in a dose-dependent manner. Propofol reduces the protein stability and nuclear localization of HIF-1α; thus, it antagonizes the effect of LPS on the activation of HIF-1α and regulates the response of cells to an inflammation-related microenvironment.[30] Therefore, propofol can potentially reduce the metastasis of tumor cells.

In summary, findings from previous in vitro studies indicate that propofol inhibits the growth and metastasis of tumors, although the mechanisms have not been fully elucidated.

Clinical Studies on the Effect of Propofol on Tumors

Only a few clinical studies have explored pulmonary metastasis after tumor resection. Notably, this was a retrospective study comprising lung cancer patients who reported better outcomes after TIVA than after inhalation anesthesia.[31] A study explored the percentage of CD4(+) and CD28(+) cells and the ratio of interferon-γ/interleukin-4 in patients with non-small-cell lung cancer after lobectomy. The findings showed that propofol promotes the activation and differentiation of T helper cells in peripheral blood, and the activation and differentiation of T helper cells plays an important role in perioperative antitumor and anti-infective immunity, indicating that propofol may have an antitumor effect.[32] Multicenter prospective clinical studies should be conducted to explore the effect of propofol anesthesia on lung metastasis.

In general, propofol has been shown to potently reduce the viability of tumor cells and postpone lung metastasis in vivo and in vitro. Its function may be mediated by regulating factors related to apoptosis, T helper cells, and some signaling pathways. These results show a new efficacy of propofol in addition to sedation and hypnosis and provide a possible strategy for tumor treatment.

Etomidate

In vitro Studies on the Effect of Etomidate on Tumors

A previous study reported that the activity of MMP-2 was reduced after treatment of A549 cells with etomidate for 48 h. In addition, etomidate downregulated the expression of PKC, MMP-7, MMP-1, MMP-9 and P-P-38, whereas the expression of RAS, PI3K and phosphorus extracellular signal-related kinases was upregulated, thus inhibiting the migration and invasion of A549 cells.[33]

Clinical Studies of the Effect of Etomidate on Tumors

Intraoperative etomidate stabilizes hemodynamics and maintains the levels of CD4+ and CD8+ cells in patients with lung adenocarcinoma,[34] which may be beneficial in preventing tumor metastasis. However, only a few clinical studies and clinical retrospective studies have explored the effect of etomidate on the clinical outcomes of cancer

patients. Therefore, further studies on etomidate using animal models and clinical observation of different cancer types should be conducted to explore the effect of etomidate.

Opioids

In addition to their analgesic properties, opioids have several nonanalgesic effects.[35] Opioids also act on tumor and immune cells, and previous studies have reported inhibition of growth in various tumor cell types by opioids. However, studies have reported both positive and negative effects of mu agonists on tumor growth; hence, further studies should be conducted.

In vivo Studies on the Effects of Opioids on Tumors

Opioids induce the proliferation of tumor cells in a concentration- and time-dependent manner. Low concentrations or single doses of opioids can stimulate tumor growth. In contrast, high concentrations or chronic opioid use inhibit tumor growth.[36]

The μ receptor is overexpressed in some non-small-cell lung cancer cells.[37] Morphine can activate the μ-opioid receptor (MOR) in tumor cells, induce phosphorylation of epidermal growth factor receptor (EGFR), and promote activation of downstream MAPK/ERK Akt, ultimately promoting cell proliferation and invasion. Morphine upregulates the expression of EGFR and MOR in lung cancer and promotes the growth of non-small-cell lung cancer. EGFR in human lung cancer indicates that morphine has a growth-promoting effect in lung cancer, thus increasing the risk of micrometastasis.[38]

Silencing of the μ receptor using a knockout technique can significantly reduce opioid-induced tumor growth in vitro.[39] Mathew et al[40] reported that the expression of the μ-opioid receptor in NSCLC cells was 5–10 times higher than that in normal lung tissue. Application of the μ-opioid receptor agonist morphine promoted the growth of Lewis lung cancer cells, whereas use of μ-opioid receptor blockers or inhibition of μ-opioid receptors inhibited the proliferation and migration of 50% to 80% of Lewis lung cancer cells. Furthermore, the study explored the relationship between opioid receptors and tumor metastasis, and the findings showed that opioid receptor knockout mice treated with the opioid receptor antagonist naltrexone had reduced lung cancer metastasis.

Methylnaltrexone (MNTX) is a selective peripheral μ receptor blocker. Use of MNTX shows similar results as naltrexone. Continuous infusion of MNTX after tumor formation significantly reduced primary tumor growth and lung metastasis.[40–42]

In vitro Studies on the Effect of Opioids on Tumors

Although morphine is the classical opioid "reference molecule", several other semisynthetic and synthetic opioids are clinically used for the management of pain in patients. Notably, different opioids have different effects on tumor metastasis.

Some studies have explored the inhibition of natural killer cell activity by fentanyl, which is important for abrogating metastasis.[43,44]

Clinical Studies on the Effects of Opioids on Cancer

Clinical studies have been conducted to explore the association between opioid use and an increased risk of tumor recurrence.[45,46] Recent studies have reported that high doses of opioids after surgery in early NSCLC patients increased the risk of tumor recurrence 5 years after video-assisted thoracoscopic surgery (VATS).[47]

A single-center retrospective study explored the effect of postoperative opioid use on overall survival (OS) and disease-free survival (DFS) in early-stage NSCLC patients. The results showed a significant decrease in overall survival in the opioid-using group compared to the control group.[48]

Similarly, Maher et al reported that postoperative opioid use increased cancer recurrence and reduced DFS in 99 patients with stage I and IIa non-small-cell lung cancer.[47]

In contrast, a previous study reported that there was no significant correlation between total opioid consumption and long-term recurrence or survival in patients after radical resection of lung cancer.[49]

Inconsistencies remain as to whether the opioids only inhibit or also promote lung cancer growth. In summary, these results indicate that morphine can stimulate the proliferation of cells with high MOR expression. For clinical implications, MOR antagonists may be worth investigating further as potential therapeutic agents in cancer therapy.

Ketamine

Ketamine is a noncompetitive blocker of nonsteroidal receptors and is the only intravenous anesthetic with definite analgesic effects. Ketamine exerts immunoregulatory effects on macrophages, lymphocytes and mast cells. Notably, 10 mg/kg ketamine inhibits NK cell activity in vitro.[44]

In vivo Studies on the Effects of Ketamine on Cancer

A study using a rat model reported that administration of ketamine at a concentration 2–3 times greater than the clinical dose inhibited dendritic cell-mediated T-cell activation.[50] Previous studies explored the effects of ketamine on NK cell activity and tumor cell metastasis in mice, and the findings showed that ketamine increased the lung metastasis ability of MADB106 cells and significantly inhibited the activity and proliferation of NK cells.[12]

Clinical Studies on the Effects of Ketamine on Cancer

Connolly et al explored the relationship between the tumor-specific genome and intraoperative opioid administration and the survival rate of patients with lung cancer. The findings showed that intraoperative opioid exposure is associated with worse overall survival, whereas ketamine exposure is associated with improved recurrence-specific survival in patients with early-stage lung adenocarcinoma.[51] Furthermore, owing to the different expression of the corresponding receptors on various tumor cell surfaces,[52] ketamine facilitates α and β adrenergic receptor activation, which may directly promote the apoptosis of tumor cells, but its role is still controversial.

Tramadol

Tramadol is a key analgesic drug with multiple analgesic mechanisms. Tramadol inhibits the reuptake of 5-HT and norepinephrine by binding to μ receptors and simultaneously activating the central monoaminergic system.

Gaspani et al[53] reported that tramadol, which is equivalent to morphine, can effectively reduce immunosuppression caused by surgical stress and pain. In addition, tramadol inhibits the growth and metastasis of tumors. Notably, it exhibits higher activity than morphine on tumor biological effects such as proliferation, apoptosis, invasion and metastasis. Tramadol inhibits the proliferation and weakens the invasive ability of A549 cells by modulating the PTEN/PI3K/AKT signaling pathway and by inducing apoptosis.[54] In addition, it can enhance the chemosensitivity of lung cancer A549 cells to cisplatin.[55] These studies provide new evidence that treatment with tramadol may play an unappreciated role in tumor progression. We hope that exploring the mechanism through which tramadol exerts its tumor progression inhibitory effects will establish a role for determining prognosis and combination antineoplastic therapy.

Midazolam

Midazolam is a short-acting benzodiazepine sedative-hypnotic drug used for sedation and for the treatment of insomnia and epilepsy. Midazolam acts by binding to the benzodiazepine binding site of the gamma-aminobutyric acid type A receptor, thus mediating its primary clinical effects. In addition, midazolam binds to peripheral benzodiazepine receptors. Peripheral benzodiazepine receptors modulate a variety of cellular functions, including cell proliferation, oxidation and apoptosis.

Wang et al[56] explored the effect of midazolam on the human lung cancer cell line A549 in vitro and in vivo. The findings indicated that midazolam inhibits the proliferation and migration of lung cancer cells in vitro and significantly downregulates the expression of Ki67 and cyclin D in xenograft mice. This may be partly mediated by peripheral benzodiazepine receptors.

A study by Makino et al reported that STAT3 plays an important role in the growth of lung cancer.[57] The role of midazolam and miR-520d-5p in the induction of apoptosis in the NSCLC cell line A549 was explored. The findings indicated that midazolam upregulates the expression of miR-520d-5p in A549 cells and inhibits the growth of tumor cells by inhibiting STAT3 activity and inducing apoptosis.

These studies have explained to some extent the positive effect of general anesthesia combined with regional nerve block on the overall survival rate of lung cancer patients.

Dexmedetomidine

Dexmedetomidine is an α2 adrenergic receptor agonist with sedative, analgesic, anxiolytic, and sympatholytic effects. Dexmedetomidine exhibits different effects on the invasion and metastasis of different cancer cells through varying mechanisms. Several studies are currently exploring the effect of dexmedetomidine on the biological behavior of cancer cells.

In vivo Studies on the Effect of Dexmedetomidine on Cancer

Wang et al found that dexmedetomidine promotes the survival of cancer cells by modulating the α2-adrenoceptor signaling pathway in lung cancer and glioma cells. However, findings from in vivo studies showed that dexmedetomidine did not have significant effects on tumor growth.[56]

Dexmedetomidine increases retention and metastatic growth of Lewis lung cancer cells in C57BL/6 mice.[58] In addition, dexmedetomidine promotes the metastasis of postoperative lung cancer cells in mice by inducing monocyte bone marrow-derived inhibitory cell proliferation and increasing the production of vascular endothelial growth factor.[59,60]

In vitro Studies on the Effect of Dexmedetomidine on Cancer

Studies report that dexmedetomidine promotes hypoxia-induced lung cancer cell progression by regulating HIF-1α signaling, which is associated with the α2 adrenergic receptor pathway.[59]

Clinical Studies on the Effect of Dexmedetomidine on Cancer

Several clinical studies report that dexmedetomidine affects the proliferation and metastasis of lung cancer cells. Dexmedetomidine induces the proliferation and inhibition of bone marrow-derived cells in postoperative patients with lung cancer. Notably, this cell group significantly promoted angiogenesis tendency score matching. Although intraoperative dexmedetomidine had no significant effect on the relapse-free survival rate of NSCLC patients, it showed an association with the overall survival rate.[60] This illustrated to a certain extent the positive effect of dexmedetomidine on the overall survival rate of lung cancer patients.

Muscle Relaxants

The relationship between muscle relaxants and lung tumor metastasis has not been fully elucidated.

However, a previous study reported that cisatracurium inhibits the proliferation of A549 lung cancer cells when administered at a concentration greater than or equal to the clinical concentration. In addition, vecuronium bromide exerts an inhibitory effect when the concentration is higher than the intubation concentration. Moreover, cisatracurium and vecuronium bromide significantly inhibit the metastasis and invasion of lung cancer cells.[61] More studies at the molecular, cellular, animal and clinical levels should be conducted to elucidate the underlying mechanism of the role of muscle relaxants in lung cancer metastasis.

Inhalation Anesthetics

Inhalation anesthetics mainly include isoflurane and sevoflurane. These drugs typically act on synapses or axonal membranes and inhibit nerve signal transduction by blocking ion transport. In addition, they inhibit the proliferation of immune cells, including NK cells and T lymphocytes. Inhalation anesthetics induce apoptosis in a dose- and time-dependent manner, reduce reconstruction of the immune system, and promote tumor proliferation, migration and recurrence.[35]

Sevoflurane

In vivo Studies on the Effect of Sevoflurane on Cancer

Pretreatment of Lewis lung cancer cells with sevoflurane inhibits lung metastasis in mice, which is attributed to the downregulation of MMP-2 and MMP-9 expression in cancer cells.[62]

Johnson et al conducted a study using a mouse breast tumor resection model and reported that lidocaine combined with sevoflurane reduces lung metastasis of breast cancer, probably through anti-inflammatory and antiangiogenic effects of the drugs.[63]

However, a previous study reported that sevoflurane (2 vol%) promotes the proliferation of Lewis lung cancer cells in vitro but has no significant effect on cell proliferation in vivo. Kim et al conducted in vivo and in vitro experiments to explore the effect of sevoflurane on the proliferation of Lewis lung cancer cells (LLCs). The findings showed that sevoflurane promotes the proliferation of LLC cells in vitro but had no significant effect on the proliferation of LLC cells in vivo. These findings indicate that the effect of anesthetics on lung cancer cells in vivo may be different from the in vitro effects.[64]

In vitro Studies on the Effects of Sevoflurane on Cancer

Sevoflurane is metabolized by cytochrome P4502E1 in lung cancer to produce toxic products that reduce the expression of CD44 and CD54 and promote apoptosis of lung cancer cells.[65] In addition, sevoflurane affects the invasive ability of non-small-cell lung cancer cells,[66] and enhances the chemosensitivity of A549 cells to cisplatin.[67,68] Sevoflurane downregulates the expression of MMP-2 and MMP-9, bundle protein and Ezi protein, which may be related to the inactivation of p38MAPK signaling pathways.[66]

In addition, placing a culture plate inoculated with an A549 single-cell suspension in a closed plexiglass box improves the invasiveness of lung cancer cells.[69] Sevoflurane also inhibits HIF-1α-induced growth and metastasis of lung cancer cells.[70] Moreover, 3%

sevoflurane significantly promotes apoptosis of A549 lung cancer cells, mainly through induction of apoptosis by regulating the expression of miRNA.[71]

Isoflurane, Desflurane, Halothane and Nitrous Oxide

Isoflurane promotes the proliferation, migration and invasion of lung cancer cells by activating the Akt-mTOR pathway.[72]

Studies report the formation of more lung tumors when desflurane-treated cancer cells are injected into mice. This effect can be attributed to the induction of EMT and cancer cell metastasis by modulation of the miR-34a/LOXL3 axis by desflurane.[73]

Shapiro et al used mouse models and reported that halothane promotes tumor progression and metastasis of lung cancer and induces liver metastasis. In addition, the findings showed that exposure to nitrous oxide for the induction of anesthesia was associated with increased metastasis of lung cancer and melanoma in surgically resected mice.[74] The present results can aid anesthesiologists in the selection of appropriate inhalation anesthetics for patients with lung cancer.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Previous studies report that cyclooxygenase (COX-2) expression is related to metastasis in multiple biological stages. The COX-2 gene is overexpressed in lung cancer, indicating that COX-2 is involved in the occurrence and development of lung cancer.[75,76] COX-2 and prostaglandin E2 (PGE2) are major causes of cancer progression.[76] As such, nonsteroidal anti-inflammatory drugs have potential anticancer effects.[77] Inhibition of PGE2 production, secondary to the inhibition of COX-2, may play an important role in the mutation and proliferation of cancer cells. In addition, inhibition of COX has an anti-inflammatory effect, enhances the immune response and inhibits cell aggregation, which is an important mechanism for tumor metastasis.[78]

Vogel et al explored the relationship between lung cancer risk and single nucleotide polymorphisms of genes involved in the inflammatory response. The findings showed that the use of NSAIDs changes the risk of lung cancer depending on genotype.[79]

The possible anticancer benefits of perioperative use of nonsteroidal anti-inflammatory drugs are only theoretical. Currently, no studies have explored the effect of nonsteroidal anti-inflammatory drugs on the survival rate or recurrence rate of cancer patients. However, as an analgesic with antitumor effects, the multimodal analgesic method using NSAIDs assisted with opioids during the perioperative period may be a new option for cancer patients to improve their clinical outcomes.

Local Anesthetics

Local anesthetics can temporarily, completely or reversibly block sensory nerve impulses and the conduction of signals, thus reducing local pain and sensation. The main mechanism of action of local anesthetics is binding to voltage-gated sodium channels, thus blocking Na^+ influx and reducing the excitability of nerve cells. These effects ultimately block nerve impulses and signal conduction. Previous studies report that local anesthetics can inhibit tumor growth.

In vitro Study

Local anesthetics, mainly amide local anesthetics, have been widely studied.[80] Lidocaine exhibits antigrowth and antimetastatic effects on lung cancer cells by upregulating miR-539 and blocking EGFR signaling via directly binding to EGFR.[81] Lidocaine and ropivacaine attenuate TNF-α-induced Src activation in pulmonary endothelial cells to maintain endothelial barrier function[82] and reduce cancer cell migration through phosphorylation of intercellular adhesion molecule-1.[83] Therapeutic concentrations of lidocaine show significant inhibition of Src phosphorylation and ICAM-1 expression in human lung cancer cells in vitro.[84] A study by Pigeler reported that inhibition of TNFα-induced Src activity and reduction of activated Src through phosphorylation can inhibit the growth and metastasis of lung cancer cells.[85]

Lidocaine, ropivacaine and bupivacaine inhibit cell proliferation and differentiation, exert cytotoxicity to mesenchymal stem cells in vitro, and play an important role in tumor growth, metastasis and development of cancer cells.[86] Studies on procaine report that low-dose procaine inhibits the proliferation of lung cancer cells; however, the effect is not observed at high doses of procaine.[87]

In vivo Studies

A study was conducted on the 4T1 mouse breast cancer model and reported that lidocaine and propofol reduced

lung metastasis on the 14th day after operation.[16] This is consistent with the results of another study.[88] Lidocaine, combined with sevoflurane anesthesia, may reduce lung metastasis through anti-inflammatory and antiangiogenic effects in a 4T1 breast cancer mouse model.

Although several experimental studies report that perioperative use of regional and local anesthetics has potential beneficial effects, the exact role and effects of local anesthetics in cancer surgery are not clear owing to the lack of clinical data from randomized controlled trials. Further studies should explore whether intravenous infusion of lidocaine improves the prognosis of cancer patients after surgery. However, it may also be an ideal adjuvant for cancer treatment.

Effects of Different Anesthetic Methods on Tumor Metastasis and Recurrence

Different anesthesia methods may affect the microenvironment of cell growth.[89] Various retrospective studies have explored the association between anesthetic regimens and tumor recurrence/metastasis and/or patient survival. The findings indicate that anesthesia regimens play important roles in tumor metastasis and/or recurrence after surgery.[90] The studies are summarized in Table 2.

Xu et al reported that different anesthesia methods affect the serum environment, thus affecting the biological behavior of tumor cells and potentially leading to metastasis of tumor cells.[91] Different anesthesia methods, including epidural anesthesia, intravenous anesthesia, inhalation anesthesia, combined intravenous-inhalation anesthesia, and intercostal nerve block, have different effects on the growth and metastasis of cancer cells.[92,93]

Total Intravenous Anesthesia

Several clinical studies report that total intravenous anesthesia (TIVA) is correlated with a longer survival rate than inhaled anesthetics in cancer surgery.[31,94–96] In contrast, retrospective analysis of lung cancer patients indicated that TIVA did not significantly improve patient prognosis compared with inhalation anesthesia.[97,98]

Regional Anesthesia and Spinal Canal Anesthesia

A retrospective clinical study reported that regional anesthesia reduces postoperative tumor recurrence.[99] Ketamine and propofol anesthesia induced more lung tumor metastases in Fischer 344 rats administered MADB106 tumor cells through the tail vein after exploratory laparotomy than intraspinal anesthesia. This finding indicates that intraspinal anesthesia is more effective than general anesthesia in protecting immune surveillance function.[5,100] Another study reported that although paravertebral block did not reduce tumor recurrence, it was correlated with a higher overall survival after lung cancer surgery.[101]

Moreover, Jingbo et al reported that a combination of epidural and general anesthesia is more effective in preventing specific short-term adverse events, improving long-term survival, maintaining hemodynamic stability, and inhibiting surgical stress-mediated inflammatory responses compared to administration of general anesthesia alone in patients with early-stage NSCLC after tumor resection.[102]

Xu et al[103] recommended a combination of general-epidural anesthesia (CGEA) for radical resection of NSCLC patients. The findings showed that postoperative CD4+ and CD4+/CD8+ values after administration of the combined anesthesia therapy were higher than those of patients administered TIVA. In addition, the combined anesthesia therapy exhibited less interference on cellular immune function than the use of TIVA.

Another study reported similar findings,[104] wherein patients undergoing radical lung cancer surgery who received TIVA combined with epidural anesthesia and epidural analgesia had less interference with the immune system and a faster recovery. Perioperative immune system function is highly correlated with the risk of postoperative infection and disease progression in cancer patients.[105,106] Therefore, minimizing factors that lead to immunosuppression is important.

Sen et al[107] explored the effects of paravertebral nerve block combined with propofol intravenous anesthesia and sevoflurane inhalation anesthesia on serum VEGF and transforming growth factor-β (TGF-β) in patients undergoing radical resection of lung cancer. The findings showed that paraspinal nerve block improves the effect of postoperative analgesia and reduces the levels of tumor

Table 2 Effects of Different Anesthetic Methods on Tumor Metastasis and Recurrence

Title	Study Authors	Year	Type	Techniques Compared	Significant Results
Effects of anaesthesia on proliferation, invasion and apoptosis of LoVo colon cancer cells in vitro.[91]	Xu YJ et al	2016	In vitro study	GA+ epidural (n = 20); INHA +opioid (n = 20)	Inhibited the proliferation and invasion of LoVo cells and induced apoptosis in GA+ epidural group
Effects of neuraxial block and general anesthesia on tumor metastasis in rats[100]	Zheng Wei et al	2008	In vivo study	Ketamine, propofol, neuraxial block.	Compared with those in group neuraxial block, CD3(+), CD4(+), CD8 (+), CD161a (+) lymphocytes the activity of circulating NK cells were significantly reduced in ketamine and Propofol; the lung metastases of MADB106 increased significantly in groups K and P (P<0.05 or 0.01).
Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery:A Retrospective Analysis.[94]	Wigmore J et al	2016	Clinical research	INHA (n =3316); TIVA (n = 3714)	INHA was associated with a hazard ratio of 1.59 (1.30 to 1.95) for death on univariate analysis and 1.46 (1.29 to 1.66) after multivariable analysis in TIVA
Impact of anesthetic agents on overall and recurrence-free survival in patients undergoing esophageal cancer surgery:A retrospective observational study[31]	Jun I.J et al	2017	Clinical research	INHA (n = 191); TIVA (n = 731)	INHA was independently associated with worse OR (HR 1.58); and RFS (HR 1.42); after multivariable analysis adjustment. in PSM cohorts, INHA was associated with worse OR (HR 1.45) and RFS (HR 1.44).
Long-Term Oncologic Outcomes for Patients Undergoing Volatile Versus Intravenous Anesthesia for Non-Small Cell Lung Cancer Surgery: A Retrospective Propensity Matching Analysis.[97]	Oh et al	2018	Clinical research	INHA (n = 194); TIVA (n = 749)	No difference in (HR) for recurrence between the TIVA and INHA groups (P =0.233); No difference in (HR) for death (P = 0.551).
A comparison of regional and general anesthesia effects on 5 year survival and cancer recurrence after transurethral resection of the bladder tumor:a retrospective analysis.[99]	Jang D et al	2016	Clinical research	GA (n=24); regional(spinal or epidural) (n=137)	Five-year survival was 87.5% for GA and 96.3% for regional (P = 0.099). Regional anesthesia showed higher 5-year survival (coefficient = −0.167,) more than GA through the partial correlation analysis.
Paravertebral block does not reduce cancer recurrence, but is related to higher overall survival in lung cancer surger: a retrospective cohort study[101]	Lee EK et al	2017	Clinical research	PCA (n = 574), TEA (n = 619), PVB (n = 536).	Analgesic method was associated with OS (P=0.0015); HR against TEA [95% confidence intervals]: PCA 0.58 PVB0.60. After PSM, PVB showed higher OR. No significant in RFS
Combined anesthesia shows better curative effect and less perioperative neuroendocrine disorder than general anesthesia in early stage NSCLC patients[102]	Pi et al	2019	Clinical research	GA (n = 76) GA+ epidural (n = 74)	Lower specific adverse events and improved OR, PFS were in GA+ epidural group; Lower MAP and levels of IL-1, IL-8, hs-CRP, TNF-α, MDA in GA group
Effects of combined general-epidural anesthesia and total intravenous anesthesia on cellular immunity and prognosis in patients with non-small cell lung cancer: A comparative study.[103]	Xu Q et al	2017	Clinical research	GA+ epidural (n =60) TIVA (n =60)	At 24 and 48 h after surgery, higher CD3+, CD4+, CD4+/CD8+ and CD56+ in group GA+ epidural, after 72h surgery, higherCD3+, CD4+, CD4+/CD8+ in group GA+ epidural.

Effects of epidural analgesia on cancer recurrence and long-term mortality in patients after non-small-cell lung cancer resection[108]	Wu et al	2019	Clinical research.	Epidural (n =1799); intravenous analgesia (n = 392)	3 year RF 69.8% and OR 92.4% in epidural group;3-year RF 67.4% and OR 89.6%in intravenous analgesia group; no significant difference in recurrence or mortality between groups, similar to the results after matching (HR: 0.97 to 1.31).
Effect of thoracic paraspinal block-propofol intravenous general anesthesia on VEGF and TGF-beta in patients receiving radical resection of lung cance[107]	Sen Y et al	2019	Clinical research	PPA(n=41); INHA(n=41)	Lower VEGF and TGFβ concentration in PPA group (P < 0.05)
A study on cellular immune function of patients treated with radical resection of pulmonary carcinoma with two different methods of anesthesia and analgesia[104]	Chen et al	2017	Clinical research	TIVA(n=17); TIVA+epidural +PCEA (n=17)	CD8+ increased and CD3+, CD4+, CD4+/CD8+ ratio and NK cells decreased in two groups;(p<0.05).

Abbreviations: BCR, biochemical recurrence; CSS, cancer specific survival; GA, general anaesthesia; HR, hazard ratio; OR, odds ratio; OS, overall survival; PCA, patient-controlled analgesia; PFS, progression-free survival; PVB, paravertebral block; RCT-PHA, RCT-post hoc analysis; PSM, the propensity score matched; RFS, recurrence-free survival; TURBT, transurethral resection of bladder tumour; PCEA, patient-controlled epidural analgesia; INH, volatile inhalational; TEA, thoracic epidural analgesia; PPA, paravertebral nerve block-propofol intravenous general anesthesia.

angiogenesis-related factors in serum. These findings indicate that regional nerve block improves postoperative stress and immunosuppression, ultimately affecting the prognosis of patients.

A large-scale retrospective study using propensity scores to evaluate the effect of epidural analgesia on tumor outcome after lung cancer surgery reported that epidural analgesia was not correlated with improvement in recurrence-free survival or overall survival in patients with non-small-cell lung cancer.[108]

Current research has shown that combined anesthesia is an ideal method that appears to be superior to general anesthesia alone in enhancing the analgesic effect, reducing the intraoperative stress response, decreasing immune suppression, and preventing tumor metastasis in patients with NSCLC. This suggests that combined anesthesia may have certain value in the treatment of lung cancer.

Table 3 provides a summary of both Anesthesia or Anesthesia on Metastasis of Lung Cancer.

Conclusion and Prospect

In summary, several factors affect the metastasis and recurrence of lung tumors, and studies report that anesthetic drugs affect cancer metastasis. The rational use of anesthetic drugs and the selection of anesthetic methods can enhance antitumor effects and reduce the risk of tumor recurrence and metastasis. Our previous in vitro studies also indicated that intravenous anesthetic agents, including propofol, sufentanil and rocuronium, inhibited the proliferation of A549 lung cancer cells. The inhibitory effect of the combination of the three drugs at clinical concentrations on cell proliferation was stronger than each one separately (unpublished data). Furthermore, our in vivo experiments demonstrated that three-drug combination treatment could also inhibit tumor growth in xenograft models (unpublished data). Our future studies should focus on investigating the interaction between anesthetics and the mechanism of the development process of lung cancer. Exploring the biological relationship between anesthetics and lung cancer, providing information on the inhibitory effect of certain anesthetic drugs on tumor micrometastasis in clinical anesthesia, and developing individualized and effective anesthetic regimens may help reduce the incidence of tumor micrometastasis and improve the postoperative survival rate of cancer patients.

Table 3 Effect of Anesthesia or Anesthesia on Metastasis of Lung Cancer

Anesthetic Factors	In vivo Study	In vitro Study	In Clinical Studies	Predominant Effects
Intravenous drug				
Propofol	*Inhibition*[16,18,19]	*Inhibition*[17,20–26]	*Inhibition*[32]	Beneficial
Etomidate		*Inhibition*[33]	*Inhibition*[34]	Beneficial
Opioids	*Activation*[38,40]	Dose-dependent,[43] depressed NK activity[44]	*Increase recurrence*[47,49]	Inconclusive
MethylInaltrexone	*Inhibition*[40,42]	*Inhibition*[40,41]		Beneficial
Ketamine	*Activation*[5,12]		*Inhibition*[51,52]	Inconclusive
Tramadol	*Inhibition*[54]			Beneficial
Midazolam	*Inhibition*[56]	*Inhibition*[56,57]		Beneficial
Dexmedetomidine	*Activation*[56]	*Inhibition*[59]	*Activation*[60]	Inconclusive
NSAIDs	*Inhibition*[79]			*Beneficial*
Muscle relaxant cisatracurium vecuronium		*Inhibition*[61]		Beneficial
Volatile agents				
Sevoflurane	*Inhibition*[62,63]	*Activation 64, inhibition*[66,69–71] *increase sensitivity to chemotherapy*[67,68]		Inconclusive
Isoflurane		Inhibition[65] activation[72]		Inconclusive
Desflurane	*Activation*[73]			Harmful
Halothane	Activation[74]			Harmful
Local anesthetics				
Lidocaine Ropivacaine Bupivacaine procaine	*Inhibition*[16,88]	*Inhibition*[81–87]		Beneficial
Anesthetic techniques				
TIVA VS inhaled anesthetics			Longer survival rate with TIVA[94] Not improve prognosis[31,97,98]	Inconclusive
PVB VS PCA VS TEA			Longer overall survival with PVB[101]	Benefit of PVB
Epidural combined general anesthesia VS general anesthesia			Improving long-term survival in Combined anesthesia[10]	Benefit of combined anesthesia
CGEA VS TIVA			Less interference with the immune system[103,104]	Benefit of CGEA
Epidural analgesia			No difference in recurrence-free survival or overall survival[108]	Inconclusive

Abbreviations: **NSAIDs**, non-steroidal anti-inflammatory drugs; **TIVA**, total intravenous anesthesia; **PVB**, paravertebral block; **TEA**, thoracic epidural analgesia; **PCA**, patient-controlled analgesia; **CGEA**, combination of general-epidural anesthesia.

Ethics Approval

None of the authors are involved in any research conducted by humans or animals in this article.

Consent to Participate

Informed consent was obtained from all participants

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; 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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