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REVIEW

Effects of Anesthesia on Postoperative Recurrence and Metastasis of Malignant Tumors

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Abstract: It is difficult to control the recurrence and metastasis of malignant tumors; furthermore, anesthesia is considered one of the main influencing factors. There has been increasing clinical attention on the effects of anesthetic drugs and methods on postoperative tumor growth and metastasis. We reviewed the effects of anesthesia on tumor recurrence and metastasis; specifically, the effects of anesthetic agents, anesthesia methods, and related factors during the perioperative period on the tumor growth and metastasis were analyzed. This study can provide reference standards for rational anesthesia formulations and cancer-related pain analgesia protocols for surgical procedures in patients with malignant tumors. Moreover, it contributes toward an experimental basis for the improvement and development of novel anesthetic agents and methods.

Keywords: anesthesia, cancer, recurrence, metastasis, prognosis, immunosuppression

Introduction

It remains difficult to control the recurrence and metastasis of malignant tumors, which could be strongly associated with multiple factors that affect prognosis, including anesthesia.[1,2] There have been several worldwide studies on the relationships between anesthetic agents and methods with cancer growth and immune function in patients with cancer.[3,4] These studies have provided valuable references for selecting anesthesia and perioperative management for patients with cancer. Different anesthetic agents have been shown to have different effects on immunity, recurrence, and metastasis in patients with cancer.[5,6] Further, different anesthesia methods, including epidural, intravenous, inhalation, and combined intravenous and inhalation anesthesia, as well as intercostal nerve block, could have different effects on cancer recurrence or metastasis.[7–9] In surgery-naïve healthy individuals, epidural anesthesia and general anesthesia were found to induce mild transient immune suppression; however, surgical stress significantly increased the risk of peri-/post-operative cancer recurrence and metastasis.[1,10] Contrastingly, epidural anesthesia reduces the risk of cancer recurrence through surgical stress reduction. Although there is no report of paravertebral block reducing cancer recurrence, it is associated with a higher overall survival rate after lung cancer surgery.[11] Therefore, anesthesia management of patients with cancer could significantly affect their long-term prognosis. Clinical studies have proposed several beneficial measures, including appropriate induction agent selection, minimal volatile anesthetic agent usage, and minimal combined use of opioids and cyclooxygenase inhibitors.[12] Moreover, other intraoperative factors, such as blood transfusion and temperature regulation, affect

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the long-term prognosis of patients with cancer.[13,14] This study aimed to review the effects of anesthetic agents, anesthesia methods, and intraoperative factors on cancer recurrence and metastasis.

Effect of Anesthetic Drugs on Cancer Recurrence and Metastasis

Intravenous Anesthetic Agents

Intravenous general anesthetic agents act on the central nervous system to achieve anesthesia.[14–16] They are currently the main agents for anesthesia induction and maintenance. Studies have shown that most intravenous general anesthetic agents can suppress immune system function and affect cancer progression (Table 1).

Propofol

Propofol is a short-acting intravenous anesthetic that is widely used as an intraoperative and postoperative sedative and hypnotic agent.[17,18] Its anesthetic effects involve direct GABAA receptor activation, which slows their channel-closing time and blocks sodium channels.[19,20] Li et al suggested that propofol-based total intravenous anesthesia (TIVA) for breast cancer surgery could reduce the risk of recurrence within the first 5 years after modified radical mastectomy.[17] Propofol anesthesia was associated with better survival in hepatectomy for hepatocellular carcinoma patients,[21] in radical prostatectomy for prostate cancer patients,[22] in patients who underwent surgery for infiltrating bladder cancer,[23] in pancreatic cancer surgery,[24] and in open intrahepatic cholangiocarcinoma surgery.[25] However, a recent retrospective cohort study showed that propofol-based TIVA was not significantly associated with a decrease in the 1-year overall or cancer-related mortality after gastric cancer surgery, as compared with inhalation anesthesia.[26,27] In addition, a randomized control trial involving more than 976 women who underwent breast cancer surgery demonstrated that no significant difference in the locoregional recurrence or overall 5-year survival rates occurred after breast surgery using desflurane or propofol anesthesia.[28] A retrospective study with 6305 patients demonstrated that propofol may have a survival advantage compared with sevoflurane among breast cancer patients.[29] However, another study showed that paravertebral block with propofol anesthesia does not improve survival compared with sevoflurane anesthesia for breast cancer surgery.[30] The inherent weaknesses of retrospective analyses were made apparent. With regard to its mechanism, propofol is considered to protect against immunosuppression during the perioperative period and has a lower inflammatory response than volatile agents.[15] Propofol can induce apoptosis by activating different signaling pathways and inhibiting cancer cell growth.[31,32] Deng et al reported that propofol could inhibit in vitro and in vivo colorectal cancer cell (CRC) migration through PI3K/AKT signaling activation and induction of epithelial-to-mesenchymal transition (EMT).[33] By downregulating transforming growth factor β1 (TGF-β1) expression, propofol effectively inhibits osteosarcoma cell proliferation and invasion, and induces their apoptosis.[34] Liu et al suggested that propofol inhibits pancreatic cancer cell (PANC-1) invasion and induces their apoptosis through microRNA (miR)-21/Slug signaling modulation.[35] Only one study found a different conclusion, whereby propofol induces the proliferation and invasion of gallbladder cancer cells.[36] Based on this, we found that an increasing number of studies have discovered that propofol plays an important role in cancer by regulating the expression of multiple signaling pathways, downstream molecules, microRNAs, and long non-coding RNAs. Emerging evidence has indicated that propofol can improve the anti-tumor effect of some small molecular compounds or chemotherapeutic drugs. Moreover, most clinical trials imply that propofol is related with better survival outcomes in cancer patients after surgery.

Ketamine

Ketamine has an immunomodulatory effect on macrophages, lymphocytes, and mast cells.[37–39] A breast cancer rat model study reported that ketamine, sodium thiopental, and inhaled anesthetic agents could promote tumor metastasis and were inversely associated with NK cell activity.[40] This effect was significantly reduced by pre-administering the β-blocker nadolol or through long-term low-dose immunostimulant administration. He et al reported that ketamine could induce anti-apoptotic protein Bcl-2 upregulation and promote breast cancer cell invasion and proliferation.[41] Contrastingly, a recent study suggested that ketamine was an N-methyl-D-aspartate (NMDA) antagonist that inhibits pancreatic cancer cell proliferation and apoptosis.[42] These indicate that ketamine has cancer-promoting effects mainly involving immune function suppression; however, its direct effect on cancer cells remains unclear.

Table 1 The Recent Studies on the Effect of Intravenous Anesthetics on Cancers

Type of Anesthetics	Anesthetics	Authors	Year	Type of Cancer (n)	Type of Research	Effect on Cancer	Relative Pathway
Intravenous anesthetics	Propofol	Liang et al[114]	2020	Colon cancer	in vitro	↓	JAK2/STAT3
	Propofol	Zheng et al[115]	2020	Non-small-cell lung cancer (NSCLC)	in vivo and in vitro	↓	miR-21/PTEN/AKT
	Propofol	Wang et al[116]	2020	Pancreatic cancer	in vitro	↓	miR-34a-E-cadherin and LOC285194
	Propofol	Liu et al[117]	2020	Gastric cancer	in vitro	↓	MicroRNA-195-5p/ Snail
	Propofol	Li et al[118]	2020	Papillary thyroid cancer	in vivo and in vitro	↓	miR-320a, HMGB1, ANRIL and Wnt/β-catenin and NF-κB
	Propofol	Yu et al[119]	2020	Pancreatic cancer	in vivo and in vitro	↓	ADAM8
	Propofol	Li et al[120]	2020	Glioma	in vitro	↓	mir-410-3p/TGFBR2
	Propofol	Su et al[121]	2020	Cardia cancer	in vitro	↓	MAPK/ERK
	Propofol	Zhang et al[122]	2020	Colon cancer	in vivo and in vitro	↓	STAT3/HOTAIR, WIF-1 and Wnt
	Propofol	Zhang et al[123]	2020	Gastric cancer	in vivo and in vitro	↓	lncRNA MALAT1/miR-30e/ATG5
	Propofol	Xu et al[34]	2016	Osteosarcoma	in vitro	↓	TGF-beta1
	Propofol	Liu et al[35]	2016	Pancreatic Cancer	in vivo	↓	miR-21
	Propofol	Xu et al[34]	2016	Glioblastoma	in vitro	↓	miR-218
	Propofol, Etomidate, Dexmedetomidine	Deng et al[33]	2016	Colorectal cancer	in vivo and in vitro	Propofol: ↓ Etomidate: ↑ Dexmedetomidine: -	(PI3K)/AKT, Epithelial-mesenchymal transition.
	Etomidate	Chu et al[124]	2019	Lung Adenocarcinoma	in vitro	↓	MMP1, MMP2, MMP7 and MMP9
	Etomidate	Chen et al[125]	2018	Brain tumor	in vitro	↓	PARP, cleaved PARP, caspase-9 and procaspase-3
	Ketamine	Hu et al[126]	2002	Colorectal cancer	in vivo and in vitro	↓	NMDA receptor-CaMK II-c-Myc
	Ketamine	Duan et al[127]	2019	Colorectal cancer	in vitro	↓	VEGF, NMDA receptor

(*Continued*)

Table 1 (Continued).

Type of Anesthetics	Anesthetics	Authors	Year	Type of Cancer (n)	Type of Research	Effect on Cancer	Relative Pathway
	Morphine	Grandhi et al[128]	2017	8 cancers	Meta-analysis	↑(Anti-angiogenesis and immunosuppression)	Unknown
	Morphine	Zhang et al[129]	2020	Esophageal carcinoma	in vitro	↑	AMPK, Epithelial-Mesenchymal Transition
	Oxycodone	Cui et al[130]	2017	Rectal cancer	Clinic trials	↑(Immunosuppression)	Unknown
	Tramadol	Gaspani et al[131]	2002	Breast cancer	in vivo	↓(NK lymphocyte, Metastasis)	Unknown
	NSAIDs	Ye et al[59]	2020	Gynecological malignancies	Retrospective study	↓	COX-2-PGE_2-EPs
	Mu agonists	Wang et al[132]	2015	Non-small-cell lung cancer (NSCLC)	Retrospective study	↑	Unknown
	Ketorolac	Retsky et al[133]	2012	Breast cancer	Meta-analysis	↓(Anti-angiogenesis and -Metastasis)	Unknown
	Naproxen	Chen et al[134]	2020	Lung cancer, Ovarian cancer, Colon cancer	in vivo and in vitro	↓	DNA injury; COX-2 and MMP-9

Notes: ↑: enhance cancer; ↓: inhibit cancer grow or metastasis.

Opioids

Given their strong analgesic effects, opioids are widely used in perioperative analgesia and treatment of postoperative pain and chronic cancer pain.[43,44] Opioid receptors are located in both neurons and immune cells; further, they can be present in several tumor cell types.[45] Opioid promotion of tumor metastasis is intricately associated with the role of μ receptors.[46,47] Opioid receptors, especially μ receptors, are expressed on vascular endothelial cells. Binding between opioids and μ receptors promotes nitric oxide production, which is involved in angiogenesis in endothelial cells, and VEGF-mediated angiogenesis.[48,49] These processes are involved in tumor proliferation, metastasis, and recurrence. In addition, opioids can activate cyclooxygenase receptors and promote prostaglandin E_2 (PGE2) production.[50,51] PGE2 has been shown to promote the production of endothelin 1, VEGF, and platelet-derived growth factors in breast cancer cells, which promotes cancer invasion and metastasis.[52] There has been inconsistency across recent reports with regard to opioid effects on patients with cancer. For example, the antitumor morphine effects mainly occur as anti-proliferative and pro-apoptotic effects on different cancer cell types.[53,54] Koodie et al found that morphine could reduce leukocyte migration across the endothelium and tumor angiogenesis in mice.[55] They suggested that morphine may be beneficial in pain management of patients with cancer through its effects on angiogenesis. It has also been reported that tramadol has an antitumor effect, revealing that tramadol use is related to enhanced postoperative outcomes in breast cancer patients.[56] Furthermore, continuous administration of morphine with high doses is more likely to inhibit tumor metastasis and growth in rodent models. In contrast, intermittent injection induces withdrawal-like conditions and activates the hypothalamic-pituitary-adrenal (HPA) axis known to facilitate cancer metastasis and progression. Therefore, not only is the type of opioid receptor potentially significant, but the method of dosing may influence whether opiate analgesia has a pro- or anti-tumor effect.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are a class of analgesics that lack steroid structures.[57] They can inhibit cyclooxygenase, reduce the

production of PG inflammatory mediators, and exert anti-inflammatory and analgesic effects.[58,59] NSAIDs are considered capable of reducing the development, recurrence, and proliferation of various cancers, including colon, breast, lung, and pancreatic cancer.[60,61] NSAIDs are able to interfere with the tumor microenvironment by increasing chemo-sensitivity and apoptosis, and reducing cell migration. Furthermore, they can protect immune system function and reduce the risk for perioperative micrometastasis, and therefore are used as preoperative analgesics widely in patients with cancer. A retrospective study reported that ketorolac improved the overall survival of patients with lung cancer (p=0.05).[62,63] Forget et al reported an independent association of the NSAID used at the beginning of surgery with a lower risk of metastasis after lung cancer surgery.[64] Furthermore, the use of ketorolac was independently associated with longer survival. Preoperative ketorolac administration resulted in a lower cancer recurrence rate.[62,64]

Inhaled Anesthetic Agents

Inhaled anesthetic agents are widely clinically used given their strong anesthetic effects and ease in adjusting the anesthesia depth.[16,65,66] They are currently widely considered to have adverse effects on patients with cancer by suppressing immunity and promoting tumor cell migration (Table 2).

Table 2 The Recent Studies on the Effect of Volatile Anesthetics on Cancers

Type of Anesthetics	Anesthetics	Authors	Year	Type of Cancer (n)	Type of Research	Effect on Cancer	Relative Pathway
Volatile anesthetics	Sevoflurane	Zhang et al[135]	2020	Cervical cancer	in vitro	↑	HDA6, PI3K/AKT-ERK1/2
	Sevoflurane	Han et al[136]	2020	Glioma	in vitro	↓	Ca^{2+}-dependent CaMKII/JNK
	Sevoflurane	Kang et al[137]	2020	Ovarian cancer	in vitro	↓	JNK and p38 MAPK
	Sevoflurane	Li et al[138]	2020	Lung cancer	in vivo	↑	IL-6/JAK/STAT3
	Sevoflurane	Zhang et al[139]	2019	Ovarian cancer	in vivo and in vitro	↓	STC1
	Sevoflurane	Xue et al[140]	2019	Cervical cancer	in vitro	↑	Ezrin and MMP2; BCL-2; BAX
	Sevoflurane	Chen et al[141]	2019	Osteosarcoma	in vitro	↓	miR-203/WNT2B/ Wnt/β-catenin
	Isoflurane	Hu et al[142]	2018	Liver cancer	in vitro	↓	NF-κB and the PI3K/ AKT
	Isoflurane	Zhu et al[74]	2016	Glioblastoma	in vitro	↑	Unknown
	Desflurane	Elias et al[143]	2015	Ovarian cancer	Retrospective study	↓	Unknown
	Sevoflurane, Thiopental	Hurmath et al[144]	2016	Glioblastoma	in vitro	↓	MMPs
	Sevoflurane, Desflurane	Bundscherer et al[145]	2019	Colon cancer	in vitro	Sevoflurane↑, Desflurane ↓	Unknown
	Desflurane, isoflurane	Cata et al[146]	2017	Glioblastoma	META analysis	-	Unknown
	Isoflurane, Sevoflurane, Desflurane	Iwasaki et al[78]	2016	Ovarian carcinoma	in vitro	↑	MMP11 and VEGF-A

Notes: ↑: enhance cancer; ↓: inhibit cancer grow or metastasis.

Sevoflurane

Sevoflurane is an inhaled anesthetic agent widely used in cancer surgery for maintaining intraoperative anesthesia.[66,67] Several retrospective studies have shown that compared with propofol anesthesia, sevoflurane anesthesia is associated with worse clinical outcomes in patients with breast, colon, rectal, and gastric cancer.[68–70] Sevoflurane can suppress the immune response by regulating cytokine expression and reducing NK cell toxicity. Compared with patients undergoing radical laparoscopic hysterectomy for cervical cancer who received propofol, those who received sevoflurane had significantly lower CD3+, CD4 +, and natural killer (NK) cell counts, as well as a lower CD4+/CD8+ ratio. Regarding the mechanism of action, Shi et al demonstrated that sevoflurane promoted the self-renewal and proliferation of glioma stem cells in vitro by regulating the hypoxia-inducible factor (HIF) pathway.[71] This suggests that sevoflurane may enhance tumor growth, and thus affect patient outcomes by inducing tumor stem cell proliferation. Sevoflurane has been shown to increase the expression of oncogenic protein markers, including HIF-2α and nuclear *p*-p38, in neck squamous cell carcinoma cells.[72] This suggests that sevoflurane may play a key role in the adverse outcomes of cancer treatments, but does not eliminate the possibility that sevoflurane has different cell biological effects in various cancer types.

Isoflurane

Isoflurane is a volatile general anesthetic agent that induces and maintains general anesthesia to eliminate behavioral responses in patients undergoing tumor resection.[66] Benzonana et al demonstrated that isoflurane upregulates the expression of hypoxia-inducible factors HIF1a and HIF2a, as well as vascular endothelial growth factor.[73] Consequently, it promotes the growth and proliferation of RCC4 renal carcinoma cells, which may contribute to increased postoperative recurrence. Notably, propofol partially reduces the malignant capacity of cancer cells by inhibiting isoflurane-triggered HIF-1α activation. Isoflurane exposure can promote cancer cell proliferation and inhibit apoptosis in glioblastoma cells.[74] Isoflurane increases non-small cell lung cancer cell proliferation via Akt-mTOR signaling pathway activation.[75] Similarly, isoflurane inhibits apoptosis through caveolin-1 expression upregulation in human colon cancer cells.[76] In summary, these phenomena suggest that treatment with isoflurane might be a factor promoting the progression of most types of cancers.

Desflurane

Desflurane can cause adverse outcomes in most patients undergoing cancer surgery; however, there is a need for further studies on the specific biological mechanisms.[65,77] Exposure of human ovarian cancer cells to 10.3% desflurane for 2 hours promotes their migration by increasing metastasis-related gene expression, including VEGF-a, MMP-11, CXC chemokine receptor 2, and TGF-β.[78] Contrastingly, Muller-Edenborn et al reported that desflurane inhibits MMP-9 release from neutrophils and inhibits the metastasis of colon cancer cells.[79] Perioperative use of low-flow desflurane reduces the inhibitory effects on neutrophils and T cells; additionally, it protects immune function.[80,81] As for desflurane, it played a pivotal role in adverse outcomes in most patients undergoing cancer surgery; further exploration of its specific biological mechanism is still warranted.

Local Anesthetic Agents

Local anesthetic agents exert their effects by blocking voltage-gated sodium channels (VGSC) on nerve cell membranes.[82] Tumor cell membranes have VGSCs, which are associated with tumor cell invasion and metastasis.[83–85] There have been recent studies carried out on the antitumor properties of local anesthetics (Table 3). Sakaguchi et al reported that clinical lidocaine concentration inhibited the proliferation of the human tongue cancer cell line CAL27 induced by serum and epidermal growth factor.[86] Moreover, lidocaine concentrations higher than those clinically applied caused direct cytotoxicity and anti-proliferative effects. Siekmann et al reported that clinical ropivacaine concentrations inhibited colon cancer cell proliferation in vitro in a dose-dependent manner.[87] Lirk et al reported that a similar lidocaine concentration caused DNA demethylation and activated tumor suppressor genes, especially in estrogen receptor-positive breast cancer cells.[88] Additionally, local anesthetic agents can promote tumor cell apoptosis. Lidocaine and bupivacaine can inhibit the MAPK signaling pathway, reduce ERK1/2 activity, upregulate p38 MAPK, and promote apoptosis in human thyroid cancer cells.[89] Intravenous lidocaine has been shown to have anti-inflammatory effects. Continuous intraoperative lidocaine infusion in patients undergoing radical hysterectomy reduces early lymphocyte apoptosis and maintains the interferon-γ/IL-4 ratio.[90] This indicates the protective role of lidocaine in cell-mediated immunity, which contributes to tumor

Table 3 The Recent Studies on the Effect of Local Anesthetics on Cancers

Type of Anesthetics	Anesthetics	Authors	Year	Type of Cancer (n)	Type of Research	Effect on Cancer	Relative Pathway
Local anesthetics	Lidocaine	Zhu et al[147]	2019	Cervical cancer	in vitro	↓	lncRNA-MEG3/miR-421/BTG1
	Lidocaine	Wall et al[148]	2019	Breast cancer	in vivo and in vitro	↓	MMP2
	Lidocaine	Sun et al[149]	2019	Lung cancer	in vitro	↓	miR-539/EGFR Axis
	Lidocaine	Dong et al[150]	2019	Lung cancer	in vitro	↓	PI3K and Rapamycin
	Lidocaine	Xia et al[151]	2019	Retinoblastoma	in vivo and in vitro	↓	miR-520a-3p/EGFR
	Lidocaine	Zhang et al[152]	2019	Gastric cancer	in vitro	↓	Bcl-2; Bax; p-p38
	Lidocaine	Xing et al[153]	2017	Hepatocellular carcinoma	in vitro	↓	Bax; protein caspase-3; Bcl-2
	Bupivacaine	Zhu et al[154]	2020	_	in vitro	↓(Anti-angiogenesis)	Akt/mTOR and AMPK
	Bupivacaine	Zhang et al[155]	2019	Neuroblastoma	in vitro	↓	miR-132
	Bupivacaine	Xuan et al[156]	2016	Ovarian cancer, Prostate cancer	in vitro	↓	GSK3β
	Procaine	Li et al[157]	2018	Gastric Cancer	in vitro	↓	DNA methylation
	Procaine	Li et al[158]	2018	Colon Cancer	in vitro	↓	ERK/MAPK/FAK; RhoA
	Procaine	Ying et al[159]	2017	Osteosarcoma	in vitro	↓	miR-133b
	Procaine	Ma et al[160]	2016	Non-small-cell lung cancer (NSCLC)	in vivo and in vitro	↓	EGFR
	Bupivacaine, Levobupivacaine	Li et al[161]	2019	Colon cancer	in vitro	↓	CHOP; Grp78
	Lidocaine, Ketamine, Metamizole	Malsy et al[162]	2019	Pancreatic carcinoma	in vitro	↓	NFATc2 and Sp1
	Lidocaine, Ropivacaine	Siekmann et al[87]	2019	Colon cancer	in vitro	High concentrations ↓; Low concentration ↑	Unknown
	Lidocaine, Ropivacaine	Wang et al[163]	2016	Non-small-cell lung cancer (NSCLC)	in vitro	Lidocaine ↓ Ropivacaine ↓	MAPK
	Lidocaine, Ropivacaine	Piegeler et al[164]	2015	Lung adenocarcinoma	in vitro	↓	MMP-9, Src

(*Continued*)

Table 3 (Continued).

Type of Anesthetics	Anesthetics	Authors	Year	Type of Cancer (n)	Type of Research	Effect on Cancer	Relative Pathway
	Lidocaine, Mepivacaine, Ropivacaine, Bupivacaine, Levobupivacaine, Chloroprocaine	Li et al[165]	2018	Breast cancer	in vitro	↓	Unknown

Notes: ↑: enhance cancer; ↓: inhibit cancer grow or metastasis.

recurrence suppression. Lidocaine is an ideal adjuvant drug for cancer treatment given its major therapeutic advantages, strong anti-inflammatory effects, and protective effects on innate immune system surveillance.[91,92] In addition, it improves the prognosis of patients with cancer. However, its use in patients with cancer warrants further clarifications and clinical validation.

Effect of Anesthesia Methods on Growth and Metastasis of Malignant Tumors

The anesthesia effect on tumor migration and invasion remains unclear. Several retrospective studies have reported that regional anesthesia reduces the risk of tumor metastasis and recurrence. This is primarily because regional anesthesia attenuates surgery-induced neuroendocrine response and reaches the central nervous system to inhibit harmful nerve impulses.[93] Therefore, it maximally suppresses the perioperative immune response. Regional anesthesia can increase NK cell activity, maintain the Th1/Th2 ratio balance, and reduce intraoperative plasma cortisol and catecholamine levels.[1,94] Compared with only general anesthesia, general anesthesia combined with epidural anesthesia improves the clinical survival rate and reduces tumor malignancy.[95] However, other previous studies have reported contrasting findings. A multi-center randomized controlled clinical study by Short et al reported that compared with general anesthesia combined with postoperative intravenous analgesia, general anesthesia combined with postoperative epidural analgesia neither reduced the risk of tumor recurrence nor prolonged the tumor-free survival period in patients who underwent abdominal cancer surgery.[96] The reduction of cancer recurrence by epidural anesthesia could be associated with systemic conditions in the body and the biological tumor characteristics. To confirm this hypothesis, there is a need for a large-sample, multi-center, randomized controlled trial with a follow-up period that allows for validation.

Furthermore, a clinical study assessed patients with primary breast cancer who underwent general anesthesia and propofol combined with intraoperative paravertebral block anesthesia.[97] The study showed that local anesthesia reduces stress response, protects immune function in patients with tumors, and reduces opioid use. In addition, vascular endothelial growth factor C, TGF-β1, acidic fibroblast growth factor, basic fibroblast growth factor, and placental growth factor levels are reduced in the veins of patients who receive propofol combined with paravertebral block anesthesia.[97] These growth factors promote angiogenesis and metastatic tumor formation, which indicates that the employed anesthesia method affects plasma levels of angiogenesis-related factors in patients with primary breast cancer, which affects tumor recurrence and metastasis.

Anesthesia-Related Factors and Cancer Recurrence and Metastasis

During the perioperative period, many factors affect cancer recurrence, including the immune system, blood transfusions, hypothermia, hyperglycemia, and postoperative pain.[98–100]

Intact Cell-Mediated Immunity

Intact cell-mediated immunity is crucial for developing resistance to tumor metastasis.[101,102] The immune response is regulated by the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Therefore, anesthesia promotes tumor metastasis through activation of the aforementioned systems and certain tumor-derived factors.[2,66,103] Activation of these systems inhibits cell-mediated immunity (CMI) and the release of catecholamines and prostaglandin E_2 (PGE2). Moreover, these factors increase the levels of

immunosuppressive cytokines, soluble factors (eg IL-4, IL-10, TGF-β, and VEGF), and pro-inflammatory cytokines (eg IL-6 and IL- 8). In addition, inhaled anesthetic agents and opioids inhibit CMI and promote tumor cell proliferation and angiogenesis. On the other hand, propofol inhibits tumor angiogenesis but not CMI. Moreover, regional anesthesia does not affect CMI and reduces surgery-induced neuroendocrine response by weakening afferent nerve conduction in the HPA axis and the sympathetic nervous system.[85,91,104] Therefore, reducing opioid usage and inhaled anesthetic agents may reduce the risk of tumor recurrence.

Intraoperative Blood Transfusion

Compared to patients who did not receive intraoperative blood transfusion, those who did had a significantly lower disease-free and overall survival rate.[105–107] Therefore, blood transfusion is an independent risk factor for determining the prognosis of patients with cancer. Contrastingly, some studies have reported that blood transfusion or immunosuppression caused by blood transfusion is not responsible for the poor postoperative prognosis.[108] Rather, they indicated that the prognosis is closely associated with the biological tumor characteristics and the systemic condition of the patient. This inconsistency could be attributed to the complexity of the response of inherent growth and metastasis tumor properties to blood transfusion, as well as differences in the population and experimental groups across the studies.

Hypothermia

Hypothermia is a body temperature dysregulation that commonly occurs during anesthesia and surgery.[109,110] Hypothermia can have several adverse effects on the body, including affecting the prognosis of patients with cancer.[111,112] Compared with normal body temperature, Benzonana et al reported that hypothermia in Wistar rats could significantly inhibit NK cell activity and increase the susceptibility to lung metastasis.[73] A study on humans by Du et al demonstrated that hypothermia could reduce Th1-type cytokine levels, increase Th2-type cytokine levels, inhibit immune cell function, and accelerate tumor progression.[113] This demonstrates that hypothermia can promote tumor recurrence.

Conclusion

To date, anesthesia is considered among the major factors affecting the recurrence and metastasis of malignant tumors. Certain anesthetic agents and methods have adverse effects on the immunity of patients with cancer, which further increases the risk of tumor recurrence and metastasis. There have been increasing studies carried out on the different effects of various anesthetic agents on malignant tumors.

Traditionally, anesthesiologists would perform sedation, anesthesia, and postoperative analgesia unsure of whether the anesthetic agents affect tumor recurrence and metastasis. Subsequent studies have confirmed the specific effects of anesthetic agents on malignant tumor metastasis and recurrence. Future studies should determine the biological relationship between anesthetic agents and malignant tumors, their interaction during anesthesia, and means of assessing anesthesia effects and mechanisms on tumor recurrence and metastasis at the cellular and molecular levels. This could contribute toward significantly improving the survival rate of patients with cancer. In addition, they could provide new standards regarding the proper use of anesthetic agents and experimental evidence for developing novel anesthetic agents and methods.

Abbreviations

TIVA, Total intravenous anesthesia; CRC, Colorectal cancer cells; PANC-1, Pancreatic cancer cells; NMDA, N-methyl-D-aspartate; PGE2, Prostaglandin E_2; NSAIDS, Non-steroidal anti-inflammatory drugs; NK, Natural killer; HIF, Hypoxia-inducible factor; VGSC, Voltage-gated sodium channels; VEGF-C, Vascular endothelial growth factor C; TGF-β1, Transforming growth factor β1; HPA, Hypothalamic-pituitary-adrenal; CMI, Cell-mediated immunity; PGE2, Prostaglandin E_2.

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Disclosure

The authors declare no competing interests for this work.

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