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Emerging effect of anesthesia on post-operative tumor recurrence and metastasis

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Abstract

Post-operative recurrence and metastasis of malignant tumors are difficult to control, which probably results from multiple factors that affect the prognosis and the undefined mechanism. Anesthesia may be an influential factor. Researchers have performed many meaningful studies on the relationship between anesthetic drugs/methods and tumor growth/immune function, which provide important references for the anesthetic selection and peri-operative management of tumor patients. Anesthetics, analgesics, and sedatives should be used with caution because their effects in post-operative patients remain controversial. This review summarizes the emerging progress on the effect of anesthesia on post-operative tumor recurrence and metastasis, particularly focusing on the effects of anesthetic drugs, anesthetic methods, and post-operative analgesia on tumor growth and metastasis. Future studies should provide strict criteria for the proper use of anesthetics in patients with malignant tumors and provide experimental evidence for the improvement and development of novel anesthetics and anesthetic methods that have the important clinical significance.

Keywords

Anesthesia, tumor recurrence, tumor metastasis, immunosuppression, NK cells, malignant, anesthetic, immune function, post-operative, analgesia

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Introduction

The effect of anesthesia on immune function in tumor patients has been broadly studied. It is generally considered that immune function, especially cellular immunity, is inhibited by anesthesia, and that this inhibition can cause post-operative infection in tumor patients and promote tumor recurrence and metastasis. Studies have shown that different anesthetic drugs can cause differential effects on immunity in tumor patients.[1] Additionally, different anesthetic methods, such as epidural anesthesia, intravenous anesthesia, inhalational anesthesia, intravenous-inhalational combined anesthesia, and intercostal nerve block could differentially affect the tumor recurrence or metastasis.[2] Epidural anesthesia or general anesthesia was found to induce a slight and transient suppression of immune function in healthy people who did not undergo surgery, but the surgical stress could largely increase the risk of peri-operative or post-operative tumor recurrence and metastasis.[3] However, spinal anesthesia was shown to reduce the risk of tumor recurrence by alleviating surgical stress.[4] A retrospective clinical study also suggested that regional anesthesia reduced post-operative tumor recurrence.[5] Although paravertebral block was not shown to reduce tumor recurrence, it was related to a higher overall survival after lung cancer surgery.[6] Therefore, anesthesia management for tumor patients may significantly affect their long-term prognosis. Clinical studies have suggested several beneficial measures, such as proper selection of inducing drugs, minimum use of volatile anesthetics, and minimal combined use of opiates and cyclooxygenase inhibitors. Other intra-operative factors, such as blood transfusion and temperature regulation, were also shown to affect the long-term prognosis of tumor patients.[7]

Malignant tumor recurrence and metastasis are difficult to control, and anesthesia has been suggested as a main influential factor. This review focuses on the effects of anesthetic drugs, anesthetic methods, and post-operative analgesia on tumor recurrence and metastasis. The authors used the following search strategy in PubMed database and Web of Science: (anesthesia OR anesthetics) AND (tumor recurrence OR metastasis) AND (immunosuppression OR immunity). All retrieved articles and relevant reviews were manually searched to find other potentially eligible studies.

Effects of anesthetic drugs on tumor recurrence and metastasis

Certain anesthetic drugs show definite effects on the immunity and tumor recurrence/metastasis (Table 1). For example, ketamine was found to inhibit natural killer (NK) cell activity;[8] thiopental was found to decrease the number of circulating NK cell and promote tumor metastasis;[9] propofol was found to inhibit matrix metalloprotein (MMP) and prevent tumor spread;[10] inhalational agents were shown to promote the apoptosis of NK cells and human T lymphocytes and accelerate tumor metastasis;[11] nitrous oxide was shown to interfere with DNA, purine, and thymidylate synthesis, inhibit neutrophil function, and promote tumor metastasis;[12,13] opioids were shown to promote angiogenesis and immunosuppression;[14,15] and non-steroidal anti-inflammatory drugs (NSAIDS) were shown to inhibit angiogenesis and tumor spread.[16] While benzodiazepines have controversial roles,[17] muscle relaxants showed no significant effect on tumor progression. Studies at the cellular level can eliminate stress- or immunity-related influence and provide a valuable theoretical basis for the preliminary screening of anesthesia

Table 1. Effects and mechanisms of general anesthetic agents on tumor progression.

Agents	Effect	Presumed mechanism of action
Ketamine	+	Inhibits NK cell activity[8]
Thiopental	+	Decreases number of circulating NK cell and promotes tumor metastasis[9]
Propofol	−	Inhibits MMP and prevents tumor spread[10]
Benzodiazepines	N	Controversial role[17]
Inhalational agents	+	Promotes apoptosis of NK cell and human T lymphocytes and promotes tumor metastasis[11]
Nitric oxide	+	Interferes with DNA, purine and thymidylate synthesis, inhibits neutrophil function, promotes tumor metastasis[12,13]
Muscle relaxants	N	No effect on tumor progression
Opioids	+	Promotes angiogenesis and immunosuppression[14,15]
NSAIDS	−	Anti-angiogenesis and inhibits tumor spread[16]

MMP, matrix metalloprotein; NSAIDS, non-steroidal anti-inflammatory drugs
"+", pro-tumor; "−", anti-tumor; "N", no definite effects

management for tumor patients, showing bright prospects in clinical application.

Some tumors were found to spread rapidly after surgery with the use of anesthetics.[18] Additionally, the tumor incidence was shown to increase in the population with long-term exposure to anesthetic gases,[19] suggesting a close relationship between anesthesia and tumors. An animal study showed that inhalational anesthetics, such as halothane, nitrous oxide, enflurane, and isoflurane, exerted different protective properties on immune function.[20] Some intravenous anesthetics such as ketamine and thiopental were shown to damage immunity in tumor patients, increase the risk of recurrence, and promote metastasis.[18,21] A clinical dose of morphine was shown to stimulate tumor cell survival, accelerate the cell cycle, stimulate endothelial cell proliferation and angiogenesis, and induce tumor nerve and blood vessel regeneration, thereby accelerating tumor growth.[22]

The effect and mechanism of different kinds of opioids on the immune function of tumor patients are presented in Table 2. For example, morphine was found to induce immunosuppression,[23] decrease T-lymphocyte proliferation,[24] and suppress Th-cell differentiation;[25] fentanyl was found to promote lymphocyte and macrophage apoptosis;[26] oxycodone was found to suppress immune function;[27] tramadol was shown to enhance NK lymphocyte activity and block tumor metastasis;[28] and sufentanil and alfentanil were shown to inhibit NK cells and suppress mitogen-triggered lymphocyte multiplication.[29] However, buprenorphine showed no intrinsic immunosuppressive activity.[30] A recent study further confirmed that morphine increased neuroepithelial cell transforming gene 1 (NET1) expression and promoted cell migration, suggesting that NET1 regulates this effect of morphine in breast cancer.[31] Another study examined the effect of different anesthetics on NK cell-mediated tumor cytotoxicity. These authors found that isoflurane and sevoflurane attenuated NK cell-mediated tumor cytotoxicity *in vitro*,[32] and NK cells underwent quantitative and functional changes after surgery. Barbiturates were found to inhibit NK cell activity at low temperatures and increase pulmonary metastasis.[33]

The use of anesthetics is a main factor that induces post-operative immunosuppression, which can further weaken

Table 2. Effects and mechanisms of different kinds of opioids on the immune function.

Opioids	Effect	Presumed mechanism of action
Morphine	+	Induces immunosuppression;[23] decreases T-lymphocyte proliferation;[24] suppresses Th-cell differentiation[25]
Fentanyl	+	Promotes the apoptosis in lymphocytes and macrophages[26]
Oxycodone	+	Suppresses the immune function[27]
Tramadol	−	Enhances NK lymphocyte activity; blocks tumor metastasis[28]
Buprenorphine	N	Devoid of any intrinsic immunosuppressive activity[30]
Sufentanil/alfentanil	+	Inhibits NK cells and suppresses mitogen-triggered lymphocyte multiplication[29]

"+", pro-tumor; "−", anti-tumor; "N", no definite effects

patients' resistance to infection, recurrence, and metastasis.[34] An animal study found that ketamine, thiopental sodium, and flurane significantly decreased NK cell activity and increased cell metastasis, except for propofol.[9] Ketamine showed the strongest ability to promote metastasis, which was significantly weakened by β-adrenoceptor blocker or small dose of chronic immune booster,[9] suggesting that the immunosuppressive effect of anesthetics, especially the inhibitory effect on NK cell activity, is a major factor to promote cell metastasis. A retrospective study analyzed breast cancer patients undergoing mastectomy and axillary lymph node dissection, and compared the tumor recurrence rate with the use of different anesthetics.[35] Opioids were shown to stimulate tumor recurrence while regional anesthesia and non-steroidal anti-inflammatory drugs improved the prognosis of tumor patients.[35] Further analysis showed that the tumor recurrence rate was low in patients receiving pre-operative ketorolac anesthesia, while other anesthetics, such as sufentanil, ketamine, and clonidine, did not significantly decrease the breast cancer recurrence rate.[35,36]

Effects of anesthetic methods on tumor recurrence and metastasis

It is reported that 90% patients undergoing surgical primary tumor excision die from post-operative tumor recurrence and metastasis. Epidural anesthesia was found to alleviate surgical stimulation, prevent immunosuppression, and reduce the dose of inhalational anesthetics and opioids, suggesting that epidural anesthesia can reduce peri-operative and post-operative tumor recurrence.[37] However, another study showed the opposite results; innate immunity was suppressed in patients with non-small cell lung cancer after surgical resection because it was not preserved by the use of peri-operative epidural anesthesia.[38] General anesthesia combined with spinal anesthesia was found to block the harmful stimulation at the surgical area and reduce regional stress, thereby decreasing tumor metastasis.[39] General anesthesia combined with intraspinal anesthesia showed a lower risk of metastasis compared with general anesthesia combined with post-operative morphine analgesia, while the recurrence rate between the two methods showed no difference.[40] General anesthesia combined with epidural anesthesia was also found to play an important role in fast-track surgery, and it mitigated the surgical stress-related impairment of anti-tumor immune response, hastened the recovery of intestinal function, and improved the long-term outcomes in colon cancer patients.[41] Another retrospective study showed that general anesthesia combined with epidural anesthesia elevated the

clinical survival rate and reduced tumor deterioration compared with general anesthesia alone.[42]

Additionally, a clinical study enrolled patients with primary breast cancer who received either standard general anesthesia or paravertebral propofol anesthesia during surgery.[43] The results showed that local anesthesia reduced the stress response, protected the immune function of tumor patients, and reduced the use of opioids, thus exerting a protective role.[43] Furthermore, venous vascular endothelium growth factor C (VEGF-C), transforming growth factor β1 (TGF-β1), fibroblast growth factor acidic (aFGF), fibroblast growth factor basic (bFGF), and placental growth factor (PIGF) concentrations decreased in patients who received paravertebral propofol anesthesia.[43] The above-mentioned growth factors promote angiogenesis and metastatic tumor formation, suggesting that the method used for anesthesia can affect the concentration of angiogenesis-related factors in the plasma in patients with primary breast cancer, and then affect tumor recurrence and metastasis. However, additional evidence generated from large-scale, multicenter, randomized controlled clinical studies is required to support the conclusion.

Effects of post-operative analgesia on tumor recurrence and metastasis

Post-operative pain often causes sensory and psychological discomfort and induces the stress response in the body and affects the autonomic nervous system and the immune system, which leads to a series of functional disorders. Epidural anesthesia combined with general anesthesia were found to relieve post-operative pain and reduce side effects without increasing the risk of flap thrombosis.[44] Inhibiting post-operative immune function promotes tumor growth and affects the prognosis of tumor patients. Additionally, a surgery-induced stress response can inhibit NK cell function and promote tumor growth. Therefore, timely and effective post-operative analgesia can alleviate physical pain for patients regulate stress response, and reduce immunosuppression, as well as decrease the risk of post-operative infection, tumor recurrence, and metastasis.[37] Epidural anesthesia did not directly inhibit NK cells, but it reduced the stress-induced NK cell inhibition, inhibited tumor growth, and, thus, improved the prognosis of tumor patients.[45] Epidural anesthesia was also found to reduce the recurrence of prostate cancer in patients with radical prostatectomy, and the possible mechanism might be that epidural anesthesia had a minor immunosuppressive effect and a higher proportion of Th1/Th2 cells compared with general anesthesia.[46] Therefore, changes in the immune function are of great significance for the post-operative recovery of tumor patients. Additionally, the effect of epidural analgesia on non-specific immunity was shown to be greater than that of specific immunity, which was beneficial in treating post-operative infection.[47] Flurbiprofen and morphine intravenous analgesia showed a protective effect on T lymphocyte subsets and NK cells compared with morphine patient controlled intravenous analgesia (PCIA) alone, which was more beneficial for patients' immune function.[48] The multimodal analgesic approach was found to reduce post-operative pain after an open radical gastrectomy procedure in patients who were anesthetized with either propofol or sevoflurane, indicating a better analgesic outcome for the propofol group, especially in the early post-operative period.[49]

Colorectal cancer is a leading cause of high morbidity and mortality worldwide, and surgical excision is the most effective method for treating colorectal cancer.[1,2]

However, surgery-induced stress can destroy patients' immunity and increase the risk of tumor recurrence and metastasis.[1] Anesthesia is reported to be an effective way to control the stress response, and recent studies have shown that anesthesia and related drugs can directly or indirectly affect the immune function of colorectal cancer patients.[50] A study in patients who underwent colorectal cancer surgery showed that no correlation existed between post-operative epidural analgesia and tumor recurrence,[51] and data analysis showed that epidural analgesia reduced tumor recurrence in elderly patients, but not in younger patients.[51] These results are opposite to the previous findings in colon cancer, breast cancer, and prostatic cancer, which suggested that local anesthesia and epidural anesthesia could reduce tumor recurrence. Although this study showed no relationship between epidural analgesia and tumor recurrence, epidural analgesia may still have certain benefits for the elderly group, suggesting that the advantage of the regional anesthesia in reducing tumor recurrence might only exist in certain tumor types.

Our study has some limitations. It is unclear if the epidural analgesia was complete, and it is also unclear if the epidural administration was stopped during the perioperative period. Additionally, some unrecorded characteristics that induce tumor recurrence might affect anesthesia management. Finally, the follow-up time was relatively short, and extending the follow-up might lead to a different result.

Conclusion

Anesthesia is currently considered to be a major factor affecting the recurrence and metastasis of malignant tumors after surgery. Certain anesthetics and anesthetic methods show disruptive effects on tumor patients' immunity and further increase the risk of tumor recurrence and metastasis. However, intravenous anesthesia with propofol has been shown to reduce the incidence of pulmonary metastasis in rats with myeloma. Thus, the differential effects of various anesthetics on malignant tumors have become a new subject in anesthetic research.

Previously, anesthesiologists conducted sedation, anesthesia or post-operative analgesia without knowing whether the anesthetics used would affect tumor recurrence and metastasis. Later studies have confirmed the specific effects of anesthetics on the metastasis and recurrence of malignant tumors. Some anesthetics exhibit inhibitory effects on NK cell activity, T cell classification, and antigen-presenting cell function, and thus increase the sensitivity to recurrence and metastasis after surgery. Therefore, anesthetics, analgesics, and sedatives should be used with caution especially in cancer patients because the use of anesthetics in peri-operation or post-operation patients remains controversial.

Future studies should focus on the biological relationship between anesthetics and malignant tumors, how they interact with each other during anesthesia, and how to reveal the effect and mechanism of anesthesia on post-operative tumor recurrence and metastasis at both the cellular and molecular levels; this would significantly improve the survival rate of cancer patients. Additionally, criteria for the proper use of anesthetics and experimental evidence for the development of novel anesthetics and anesthesia methods should be provided, which would have important clinical significance.

Declaration of conflicting interest

Author Weilian Wang declares that he has no conflict of interest. Author Jinliang Xiao declares that he has no conflict of interest. Author Shuwei Shen declares that he has no

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Ethical approval

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