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. 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. 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. However, spinal anesthesia was shown to reduce the risk of tumor recurrence by alleviating surgical stress. A retrospective clinical study also suggested that regional anesthesia reduced post-operative tumor recurrence. Although paravertebral block was not shown to reduce tumor recurrence, it was related to a higher overall survival after lung cancer surgery. 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.

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; thiopental was found to decrease the number of circulating NK cell and promote tumor metastasis; propofol was found to inhibit matrix metalloprotein (MMP) and prevent tumor spread; inhalational agents were shown to promote the apoptosis of NK cells and human T lymphocytes and accelerate tumor metastasis; nitrous oxide was shown to interfere with DNA, purine, and thymidylate synthesis, inhibit neutrophil function, and promote tumor metastasis; opioids were shown to promote angiogenesis and immunosuppression; and non-steroidal anti-inflammatory drugs (NSAIDS) were shown to inhibit angiogenesis and tumor spread. While benzodiazepines have controversial roles, 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.
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
patients’ resistance to infection, recurrence, and metastasis. An animal study found that ketamine, thiopental sodium, and flurane significantly decreased NK cell activity and increased cell metastasis, except for propofol. Ketamine showed the strongest ability to promote metastasis, which was significantly weakened by β-adrenoceptor blocker or small dose of chronic immune booster, 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. Opioids were shown to stimulate tumor recurrence while regional anesthesia and non-steroidal anti-inflammatory drugs improved the prognosis of tumor patients. 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.

### 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. 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. 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. 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. 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. Another retrospective study showed that general anesthesia combined with epidural anesthesia elevated the

| Opioids                  | Effect | Presumed mechanism of action                                         |
|-------------------------|--------|------------------------------------------------------------------------|
| Morphine                | +      | Induces immunosuppression;23 decreases T-lymphocyte proliferation; suppresses Th-cell differentiation |
| Fentanyl                | +      | Promotes the apoptosis in lymphocytes and macrophages26              |
| Oxycodone               | +      | Suppresses the immune function27                                       |
| Tramadol                | −      | Enhances NK lymphocyte activity; blocks tumor metastasis28            |
| Buprenorphine           | N      | Devoid of any intrinsic immunosuppressive activity30                  |
| Sufentanil/alfentanil   | +      | Inhibits NK cells and suppresses mitogen-triggered lymphocyte multiplication29 |

“+”, pro-tumor; “−”, anti-tumor; “N”, no definite effects
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. 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. A study in patients who underwent colorectal cancer surgery showed that no correlation existed between post-operative epidural analgesia and tumor recurrence, and data analysis showed that epidural analgesia reduced tumor recurrence in elderly patients, but not in younger patients. 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 peri-operative 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
conflict of interest. Author Shu Wang declares that he has no conflict of interest. Author Minghao Chen declares that he has no conflict of interest. Author Ya Hu declares that she has no conflict of interest.

Ethical approval
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References
1. Anderson SL, Duke-Novakovski T and Singh B. The immune response to anesthe-sia: part 2 sedatives, opioids, and injectable anesthetic agents. Vet Anaesth Analg 2014; 41: 553–566.
2. Byrne K, Levins KJ and Buggy DJ. Can anesthetic-analgesic technique during prima-ry cancer surgery affect recurrence or metastasis? Can J Anaesth 2016; 63: 184–192.
3. O’Dwyer MJ, Owen HC and Torrance HD. The peri-operative immune response. Curr Opin Crit Care 2015; 21: 336–342.
4. Koumpan Y, Jaeger M, Mizubuti GB, et al. Spinal anesthesia is associated with lower recurrence rates after resection of nonmuscle invasive bladder cancer. J Urol 2018; 199: 940–946.
5. Jang D, Lim CS, Shin YS, et al. 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. BMC Anesthesiol 2016; 16: 16.
6. Lee EK, Ahn HJ, Zo JI, et al. Paravertebral block does not reduce cancer recurrence, but is related to higher overall survival in lung cancer surgery: a retrospective cohort study. Anesth Analg 2017; 125: 1322–1328.
7. Liu X, Ma M, Huang H, et al. Effect of peri-operative blood transfusion on prognosis of patients with gastric cancer: a retrospective analysis of a single center database. BMC Cancer 2018; 18: 649.
8. Shakhar G and Ben-Eliyahu S. In vivo beta-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats. J Immunol 1998; 160: 3251–3258.
9. Melamed R, Bar-Yosef S, Shakhar G, et al. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by pro-pofol: mediating mechanisms and prophylactic measures. Anesth Analg 2003; 97: 1331–1339.
10. Miao Y, Zhang Y, Wan H, et al. GABA-receptor agonist, propofol inhibits invasion of colon carcinoma cells. Biomed Pharmacother 2010; 64: 583–588.
11. Tavare AN, Perry NJ, Benzonana LL, et al. Cancer recurrence after surgery: direct to indirect effects of anesthetic agents. Int J Cancer 2012; 130: 1237–1250.
12. Weimann J. Toxicity of nitrous oxide. Best Pract Res Clin Anaesthesiol 2003; 17: 47–61.
13. Shapiro J, Jersky J, Katzav S, et al. Anaesthetic drugs accelerate the progression of post-operative metastasis of mouse tumors. J Clin Invest 1981; 68: 678–685.
14. Trapaidze N, Gomes I, Cvejic S, et al. Opioid receptor endocytosis and activation of MAP kinase pathway. Brain Res Mol Brain Res 2000; 76: 220–228.
15. Cata JP, Gottumukkala V and Sessler DI. How regional analgesia might reduce post-operative cancer recurrence. Eur J Pain Suppl 2011; 5: 345–355.
16. Retsky M, Rogers R, Demicheli R, et al. NSAID analgesic ketorolac used peri-operatively may suppress early breast cancer relapse: particular relevance to triple negative subgroup. Breast Cancer Res Treat 2012; 134: 881–888.
17. Halapy E, Kreiger N, Cotterchio M, et al. Benzodiazepines and risk for breast cancer. Ann Epidemiol 2006; 16: 632–636.
18. Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. J Transl Med 2018; 16: 8.
19. Votta-Velis EG, Piegeler T, Minshall RD, et al. Regional anaesthesia and cancer metastasis: the implication of local anaesthetics. *Acta Anaesthesiol Scand* 2013; 57: 1211–1229.

20. Strosing KM, Faller S, Gyllenram V, et al. Inhaled anesthetics exert different protective properties in a mouse model of ventilator-induced lung injury. *Anesth Analg* 2016; 123: 143–151.

21. Deng F, Ouyang M, Wang X, et al. Differential role of intravenous anesthetics in colorectal cancer progression: implications for clinical application. *Oncotarget* 2016; 7: 77087–77095.

22. Juneja R. Opioids and cancer recurrence. *Curr Opin Support Palliat Care* 2014; 8: 91–101.

23. Das J, Kumar S, Khanna S, et al. Are we causing the recurrence-impact of perioperative period on long-term cancer prognosis: review of current evidence and practice. *J Anaesthesiol Clin Pharmacol* 2014; 30: 153–159.

24. Sacerdote P, Bianchi M, Gaspani L, et al. The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesth Analg* 2000; 90: 1411–1414.

25. Gao M, Sun J, Jin W, et al. Morphine, but not ketamine, decreases the ratio of Th1/Th2 in CD4-positive cells through T-bet and GATA3. *Inflammation* 2012; 35: 1069–1077.

26. Singhal PC, Sharma P, Kapasi AA, et al. Morphine enhances macrophage apoptosis. *J Immunol* 1998; 160: 1886–1893.

27. Cui JH, Jiang WW, Liao YJ, et al. Effects of oxycodone on immune function in patients undergoing radical resection of rectal cancer under general anesthesia. *Medicine (Baltimore)* 2017; 96: e7519.

28. Gaspani L, Bianchi M, Limiroti E, et al. The analgesic drug tramadol prevents the effect of surgery on natural killer cell activity and metastatic colonization in rats. *J Neuroimmunol* 2002; 129: 18–24.

29. Shavit Y, Ben-Eliyahu S, Zeidel A, et al. Effect of fentanyl on natural killer cell activity and on resistance to tumour metastasis in rats. Dose and timing study. *Neuroimmunomodulation* 2004; 11: 255–260.

30. Boland JW and Pockley AG. Influence of opioids on immune function in patients with cancer pain: from bench to bedside. *Br J Pharmacol* 2018; 175: 2726–2736.

31. Ecimovic P, Murray D, Doran P, et al. Direct effect of morphine on breast cancer cell function in vitro: role of the NET1 gene. *Br J Anaesth* 2011; 107: 916–923.

32. Tazawa K, Koutsogiannaki S, Chamberlain M, et al. The effect of different anesthetics on tumor cytotoxicity by natural killer cells. *Toxicol Lett* 2017; 266: 23–31.

33. Ben-Eliyahu S, Shakhar G, Rosenne E, et al. Hypothermia in barbiturate-anesthetized rats suppresses natural killer cell activity and compromises resistance to tumor metastasis: a role for adrenergic mechanisms. *Anaesthesiology* 1999; 91: 732–740.

34. Amodeo G, Bugada D, Franchi S, et al. Immune function after major surgical interventions: the effect of post-operative pain treatment. *J Pain Res* 2018; 11: 1297–1305.

35. Forget P, Vandenhende J, Berliere M, et al. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. *Anesth Analg* 2010; 110: 1630–1635.

36. Tedore T. Regional anaesthesia and analgesia: relationship to cancer recurrence and survival. *Br J Anaesth* 2015; 115: ii34–ii45.

37. Kim R. Anesthetic technique for cancer surgery: harm or benefit for cancer recurrence? *Eur J Surg Oncol* 2018; 44: 557–558.

38. Cata JP, Bauer M, Sokari T, et al. Effects of surgery, general anesthesia, and perioperative epidural analgesia on the immune function of patients with non-small cell lung cancer. *J Clin Anesth* 2013; 25: 255–262.

39. Tseng KS, Kulkarni S, Humphreys EB, et al. Spinal anesthesia does not impact prostate cancer recurrence in a cohort of men undergoing radical prostatectomy: an observational study. *Reg Anesth Pain Med* 2014; 39: 284–288.

40. Exadaktylos AK, Buggy DJ, Moriarty DC, et al. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 2006; 105: 660–664.

41. Chen WK, Ren L, Wei Y, et al. General anesthesia combined with epidural
anesthesia ameliorates the effect of fast-track surgery by mitigating immunosuppression and facilitating intestinal functional recovery in colon cancer patients. *Int J Colorectal Dis* 2015; 30: 475–481.

42. Wuethrich PY, Hsu Schmitz SF, Kessler TM, et al. Potential influence of the anesthetic technique used during open radical prostatectomy on prostate cancer-related outcome: a retrospective study. *Anesthesiology* 2010; 113: 570–576.

43. Looney M, Doran P and Buggy DJ. Effect of anesthetic technique on serum vascular endothelial growth factor C and transforming growth factor β in women undergoing anesthesia and surgery for breast cancer. *Anesthesiology* 2010; 113: 1118–1125.

44. Lou F, Sun Z, Huang N, et al. Epidural combined with general anesthesia versus general anesthesia alone in patients undergoing free flap breast reconstruction. *Plast Reconstr Surg* 2016; 137: 502e–509e.

45. Procopio MA, Rassias AJ, DeLeo JA, et al. The in vivo effects of general and epidural anesthesia on human immune function. *Anesth Analg* 2001; 93: 460–465.

46. Sprung J, Scavonetto F, Yeoh TY, et al. Outcomes after radical prostatectomy for cancer: a comparison between general anesthesia and epidural anesthesia with fentanyl analgesia: a matched cohort study. *Anesth Analg* 2014; 119: 859–866.

47. Volk T, Schenk M, Voigt K, et al. Postoperative epidural anesthesia preserves lymphocyte, but not monocyte, immune function after major spine surgery. *Anesth Analg* 2004; 98: 1086–1092.

48. Wang ZY, Wang CQ, Yang JJ, et al. Which has the least immunity depression during post-operative analgesia–morphine, tramadol, or tramadol with lornoxicam? *Clin Chim Acta* 2006; 369: 40–45.

49. Ji FH, Wang D, Zhang J, et al. Effects of propofol anesthesia versus sevoflurane anesthesia on post-operative pain after radical gastrectomy: a randomized controlled trial. *J Pain Res* 2018; 11: 1247–1254.

50. Dang Y, Shi X, Xu W, et al. The effect of anesthesia on the immune system in colorectal cancer patients. *Can J Gastroenterol Hepatol* 2018; 2018: 7940603.

51. Gottschalk A, Ford JG, Regelin CC, et al. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. *Anesthesiology* 2010; 113: 27–34.