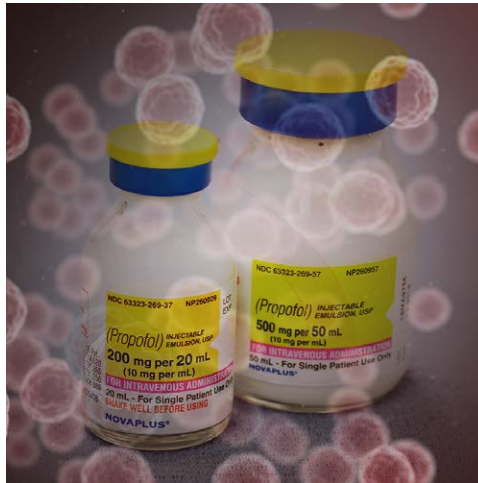


Anesthetic Drugs and Cancer Progression

Fact or Fiction

Juan P. Cata, M.D., Anil K. Sood, M.D., Holger K. Eltzschig, M.D., Ph.D.

THERE has been growing interest in understanding whether perioperative events such as short-term exposure to a general anesthesia could have a deleterious effect on the oncologic outcomes of cancer surgery by promoting growth and progression of the so-called minimally residual disease. Specifically, it has been hypothesized that the use of volatile anesthetics could be associated with minimally residual disease proliferation, whereas propofol could promote apoptosis and have antimetastatic effects.¹ In this issue of ANESTHESIOLOGY, Makito *et al.*² report the results of a retrospective study evaluating the association between overall or recurrence-free survival after cancer surgery and the use of propofol-based total intravenous anesthesia *versus* volatile anesthetic-based general anesthesia. This cohort study included cancer patients who underwent esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatotomy, colectomy, and rectal cancer surgery.² Makito *et al.* have to be commended for conducting this thorough and large-scale retrospective study that included 196,303 oncologic surgery patients in their analysis. Briefly, they showed that the use of propofol-based anesthesia in comparison with volatile-based general anesthesia was not associated with significant improvements in recurrence-free (hazard ratio, 1.00; 95% CI, 0.96 to 1.05; $P = 0.94$) or overall survival (hazard ratio, 1.01; 95% CI, 0.79 to 1.21; $P = 0.77$) after adjusting and matching patients for several factors known to impact cancer recurrence.³ The authors also conducted an instrumental variable analyses that indicated a



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the modulatory effects of general anesthesia on the stress response associated with relatively small surgical procedures such as mastectomies may not matter.⁵ In fact, Makito *et al.*'s results suggest that the general anesthesia technique used in more extensive cancer surgeries is also irrelevant to modify factors (*i.e.*, immunity) that influence oncological outcomes.

One of the main strengths of Makito *et al.*'s study is the large number of patients included in the analysis. This study currently represents the largest retrospective analysis investigating the impact of propofol-based anesthesia *versus* volatile-based general anesthesia on oncological outcomes using data from the Japanese Diagnosis Procedure

small difference in recurrence-free survival (hazard ratio, 0.92; 95% CI, 0.87 to 0.98; $P = 0.01$) but not in overall survival (hazard ratio, 1.02; 95% CI, 0.95 to 1.09; $P = 0.65$).

These findings are in sharp contrast to those from a previous study conducted by Wigmore *et al.*⁴ Although both studies were retrospective, the most striking differences are the sample sizes and the source of data. The retrospective study by Makito *et al.* evaluated 196,303 patients, whereas that by Wigmore evaluated 11,395 patients. Makito *et al.* used a national administrative registry, whereas Wigmore *et al.* reported results from a single institution. Findings from single-center studies are known to suffer from external validity. In addition, Makito *et al.*'s work is in line with a *post hoc* analysis of a recent international randomized, controlled trial indicating that the use of sevoflurane did not impact breast cancer progression.⁵ It has been recently suggested that

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Combination database. Although the information contained in that database is standardized, potential weaknesses include the possibility of sampling bias and limited accuracy of information. Makito *et al.* used a variety of strategies in their statistical analysis to limit confounding and biases. Another strength of the study is that the authors adjusted for multiple factors that are known to affect cancer progression and survival, including the administration of neoadjuvant and adjuvant therapies, perioperative blood transfusions, functional status (Barthel's index) and postoperative complications. Unfortunately, previous studies had limited information or could not adjust for those important factors, which highlights the superior quality of the study by Makito *et al.*²

Cancer growth and progression is a complex and highly orchestrated process. The objective of administering adjuvant therapies (*i.e.*, chemotherapy or radiation) is to eliminate or at least control the growth of the minimally residual disease; however, it is poorly understood whether the cellular events triggered during surgery and anesthesia in cancer cells are blunted or exaggerated by adjuvant therapies which can confound the effect of anesthetics on survival outcomes. The *in vitro* cellular effects of anesthetics on various steps of the metastasis process have been well documented. Unfortunately, well-designed experimental studies indicate that such effects are difficult to reproduce *in vivo* under experimental conditions that resemble major cancer surgery in humans.⁶ Perhaps one way to bridge the gap between laboratory *in vitro* studies and clinical research is the use of humanized mice models. In such models, tumors grow in mice implanted with human hematopoietic stem cells. Then, these cells will colonize the bone marrow and differentiate into the multiple cell lineages that constitute the human immune system. Using humanized mice models, researchers would have the opportunity to test any potential impact of the combination of surgery and anesthetics on cancer progression.⁷ To date, there is no evidence from randomized clinical trials indicating that propofol-based anesthesia is superior to volatile-based anesthesia in terms of oncological outcomes.

In summary, current evidence suggests that volatile anesthetics do not affect cancer-related outcomes in a negative fashion or impact the survival of surgical cancer patients. In other words, the practice of using propofol-based anesthesia during oncologic surgery with the goal to reduce cancer recurrence or metastatic disease is no longer supported by the available evidence. Therefore, anesthesiologists should not be using propofol-based anesthesia to improve oncologic outcomes.

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Competing Interests

Dr. Sood reports the following competing interests: Merck (Kenilworth, New Jersey, scientific advisory board), Kiyatec (Greenville, South Carolina, consulting), M-Trap (Oak Ridge, Tennessee, research grant), and BioPath (Bellaire, Texas, shareholder). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Cata: jcata@mdanderson.org

References

1. Sessler DI, Riedel B: Anesthesia and cancer recurrence: Context for divergent study outcomes. *ANESTHESIOLOGY* 2019; 130:3–5
2. Makito K, Matsui H, Fushimi K, Yasunaga H: Volatile *versus* total intravenous anesthesia for cancer prognosis in patients having digestive cancer surgery: A nationwide retrospective cohort study. *ANESTHESIOLOGY* 2020; 133:764–73
3. Matsuda S, Fujimori K, Kuwabara K, Ishikawa KB, Fushimi K: Diagnosis procedure combination as an infrastructure for the clinical study. *Asian Pacific Journal of Disease Management* 2011; 5: 81–7
4. Wigmore TJ, Mohammed K, Jhanji S: Long-term survival for patients undergoing volatile *versus* IV anesthesia for cancer surgery: A retrospective analysis. *ANESTHESIOLOGY* 2016; 124:69–79
5. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, Mayers DB, Meyer-Treschan TA, Grady M, Tan EY, Ayad S, Mascha EJ, Buggy DJ; Breast Cancer Recurrence Collaboration: Recurrence of breast cancer after regional or general anaesthesia: A randomised controlled trial. *Lancet* 2019; 394:1807–15
6. Afsharimani B, Doornebal CW, Cabot PJ, Hollmann MW, Parat MO: Comparison and analysis of the animal models used to study the effect of morphine on tumour growth and metastasis. *Br J Pharmacol* 2015; 172:251–9
7. Shultz LD, Ishikawa F, Greiner DL: Humanized mice in translational biomedical research. *Nat Rev Immunol* 2007; 7:118–30