VIEWPOINT

Can Anesthesia Influence Cancer Outcomes After Surgery?

Nicholas J. S. Perry, MBBS, BSc
Signalling & Cancer Metabolism Team, Division of Cancer Biology, The Institute of Cancer Research, London, United Kingdom.

Donal Buggy, MD, MSc, FRCPI, FFSEM, FCAI, FRCA
Department of Anaesthesia, Mater University Hospital, University College Dublin, Ireland.

Daqing Ma, MD, PhD, FRCA
Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea & Westminster Hospital, London, United Kingdom.

Corresponding Author: Daqing Ma, MD, PhD, FRCA, Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea & Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom (d.ma@imperial.ac.uk).

Surgery and pain induce stress and inflammatory responses that have radical effects on cellular and systems physiology, extending well beyond the time of surgery. There is a growing appreciation that, in the same way that mitigating the negative effects of such factors plays an important role in promoting wound healing and preventing complications (such as postoperative infections), surgery, anesthesia, and pain might also be associated with the risk of metastatic recurrence after cancer surgery. Naturally, speculation has followed that modifications of perioperative interventions, such as anesthetic or analgesic technique, may help reduce the postoperative incidence of metastasis and improve patients' long-term survival.

While at first it may be tempting to challenge the long-term importance of anesthesia in the context of a chronic, highly heterogeneous, and fundamentally genetic disease, it is worth considering how short-term events and ensuing physiological disturbances during the perioperative period might influence the fate of any minimal residual cancer, which is an undetectable population of cancerous cells persisting after surgery as a result of incomplete surgical clearance; intraoperative seeding of malignant cells into the surgical field, blood, and lymphatic fluids (as with circulating tumor cells); or the existence of subclinical micrometastatic disease prior to surgery. Whether these cells die, lie quiescent, or colonize and proliferate to emerge as new metastatic disease is thought to depend on a complex interplay of tumor-associated, microenvironmental, and immunity-associated factors. There is a certain level of experimental evidence that anesthetic drugs, opioids, blood transfusion, and other perioperative interventions may disrupt this delicate balance at a critical time of immunological susceptibility.

One of the leading lines of enquiry to have arisen from the emerging field of onco-anesthesia centers around the effect of general anesthetic drugs on cancer cell biology and host antitumor immunity. An expanding body of experimental data has evolved from more than 30 years of study into the conditioning effects of anesthetics in specialized organ tissues subjected to ischemia-reperfusion injury to suggest that general anesthetic agents also have the capacity to directly influence hallmark cancer-cell phenotypes and metastatic potential. Importantly, there appear to be notable differences in this respect between the 2 major classes of general anesthetics in clinical use today: inhalational fluorinated hydrocarbons, such as isoflurane or sevoflurane, and intravenous propofol. Inhalational agents continue to account for nearly all general anesthetics given worldwide, but recent laboratory studies have shown these to enhance angiogenesis, migration, invasion, proliferation, and chemoresistance across a range of cancer cell types. Further work is required to fully understand the molecular mechanisms driving these phenotypes and determine the extent of their influence in vivo, but the strongest evidence to date points toward a capacity to potentiate oncogenic phosphoinositide 3-kinase (PI3K), protein kinase B (also known as Akt), and mammalian target of rapamycin (mTOR) cell signaling and up-regulate hypoxia-inducible factors, with effects sustained for as long as 24 hours after a 2-hour exposure.[1] In addition to their effects on cancer cells, inhalational anesthetics also directly impair the effector functions of immune cells that play key roles in tumor cell surveillance and elimination, leading to reduced tumor cell killing in vitro and enhanced experimental metastasis in vivo.[2] In contrast, propofol, which is commonly used to maintain anesthesia by way of a continuous intravenous infusion, has been shown to antagonize those same cancer cells–signaling pathways[1]; inhibit cancer cell migration, invasion, and metastasis by reducing the synthesis of matrix metalloproteinases and impeding cell motility machinery[3]; and spare the deleterious effects of inhalational agents on cell-mediated immunity.[2,4] Its anti-inflammatory and antioxidant properties may underpin these antitumoral effects and play a role in offsetting the systemic inflammatory response elicited by major surgery, thereby potentially disrupting a major axis by which circulating tumor cells colonize distant sites and evade antitumor immune killing.[5]

Potentially in keeping with the diverging phenotypes observed in the laboratory between the 2 anesthetics, several recent retrospective clinical studies[6,7] have shown an association between inhalational anesthesia and reduced long-term survival or recurrence-free survival in patients with cancer who are undergoing elective surgery compared with survival in similar patients who receive propofol-based anesthesia. The largest and most balanced of these[6] analyzed the outcomes of 7030 patients with more than 20 different types of cancer at a tertiary cancer center in the United Kingdom and, after propensity matching and adjustment for confounding factors, reported a hazard ratio of 1.46 (95% CI, 1.29-1.66) for death at 5 years in patients receiving a general anesthetic with isoflurane or sevoflurane compared with a total intravenous technique with propofol and the ultra–short-acting opioid drug remifentanil. Although retrospective and single-center in nature, with all the inherent biases and limitations that entails, these results are consistent with the aforementioned basic science data and have already sparked debate within the specialty as to whether it is yet appropriate or justified to switch to a total intravenous anesthetic for patients undergoing cancer opera-

tions. Most anesthetists would agree that the clinical evidence base is not yet sufficiently robust to support such a move, and it should be acknowledged that there are also some small-scale studies showing no difference in outcome. However, the popularity of and familiarity with propofol-based anesthesia is steadily increasing, with advocates of the technique pointing toward other favorable characteristics, including a reduced incidence of postoperative nausea and vomiting, smoother emergence to consciousness, and more rapid recovery. Nevertheless, future prospective and multicenter trials with large sample sizes are urgently needed.

In addition to the potential outcomes of general anesthetic drugs, there are also a number of inexpensive and readily available therapeutic adjuncts that may be safely used during the perioperative period to help tackle the potential risks of disease progression. β-Adrenoceptor antagonists, nonsteroidal anti-inflammatory drugs, and antithrombotic drugs are currently under evaluation in the laboratory and clinical trials.[5] Meanwhile, promising, novel antimetastatic properties have also been attributed to amide local anesthetics, such as lidocaine. These drugs prevent nerve conduction via voltage-gated sodium channel inhibition and in this way have been shown to inhibit the invasive potential of metastatic cells that functionally express these channels.[8] Their potentially beneficial effect in cancer cells is also mediated by Src inhibition, which prevents release of mediators of cancer cell migration and metastasis.[9] Lidocaine also suppresses proliferation of cancer cells via a direct inhibitory effect on the epidermal growth factor receptor, a tyrosine kinase receptor essential for the proliferation and differentiation of tumors of epithelial cell origin.[10] Given that intravenous infusions of lidocaine are an increasingly popular constituent of multimodal analgesic regimens, particularly for major surgeries (such as laparotomy), this represents a feasible and attractive adjunct.

Taken together, these scientific data should act as a catalyst for prospective, randomized clinical trials to provide much-needed clarity as to whether the tailored use of anesthetic drugs or adjuncts, such as propofol and intravenous lidocaine, can help to improve long-term oncological outcomes. Such trials will not be straightforward, given the complexity and diversity of factors that confound the perioperative period. However, the quest to define an anesthetic technique that promotes rather than undermines efforts to prolong postoperative cancer-free survival is now an urgent priority; when scaled, it may have the potential to rapidly and affordably improve postoperative cancer outcomes worldwide.

ARTICLE INFORMATION

Published Online: January 16, 2019. doi:10.1001/jamasurg.2018.4619

Conflict of Interest Disclosures: Dr Ma reports receiving a British Oxygen Company Chair grant of the Royal College of Anaesthetists. Dr Buggy reports receiving funds from the Eccles Breast Cancer Research Fund. Drs Buggy and Ma together also report receiving a European Cooperation in Science and Technology (COST) Action grant (grant CA15204). No other disclosures were reported.

Funding/Support: The work was supported by a Cancer Research UK Clinical Research Fellowship (Dr Perry).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Alex S. Evers, MD, Washington University School of Medicine, St Louis, Missouri, for his critical comments during manuscript preparation. He was not compensated for his contribution.

REFERENCES

1. Huang H, Benzonana LL, Zhao H, et al. Prostate cancer cell malignancy via modulation of HIF-1α pathway with isoflurane and propofol alone and in combination. *Br J Cancer*. 2014;111(7):1338-1349. doi:10.1038/bjc.2014.426

2. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. *Anesth Analg*. 2003;97(5):1331-1339. doi:10.1213/01.ANE.0000082995.44040.07

3. Mammoto T, Mukai M, Mammoto A, et al. Intravenous anesthetic, propofol inhibits invasion of cancer cells. *Cancer Lett*. 2002;184(2):165-170. doi:10.1016/S0304-3835(02)00210-0

4. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study. *Br J Anaesth*. 2014;113(suppl 1):i56-i62. doi:10.1093/bja/aeu200

5. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. *Nat Rev Clin Oncol*. 2018;15(4):205-218. doi:10.1038/nrclinonc.2017.194

6. 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(1):69-79. doi:10.1097/ALN.0000000000000936

7. Jun IJ, Jo JY, Kim JI, et al. Impact of anesthetic agents on overall and recurrence-free survival in patients undergoing esophageal cancer surgery: a retrospective observational study. *Sci Rep*. 2017;7(1):14020. doi:10.1038/s41598-017-14147-9

8. House CD, Wang BD, Ceniccola K, et al. Voltage-gated Na+ channel activity increases colon cancer transcriptional activity and invasion via persistent MAPK signaling. *Sci Rep*. 2015;5:11541. doi:10.1038/srep11541

9. Piegeler T, Schläpfer M, Dull RO, et al. Clinically relevant concentrations of lidocaine and ropivacaine inhibit TNFα-induced invasion of lung adenocarcinoma cells in vitro by blocking the activation of Akt and focal adhesion kinase. *Br J Anaesth*. 2015;115(5):784-791. doi:10.1093/bja/aev341

10. Sakaguchi M, Kuroda Y, Hirose M. The antiproliferative effect of lidocaine on human tongue cancer cells with inhibition of the activity of epidermal growth factor receptor. *Anesth Analg*. 2006;102(4):1103-1107. doi:10.1213/01.ane.0000198330.84341.35