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IN ANESTHESIOLOGY AND CRITICAL CARE

ARTICLE OF THE MONTH

Brain Cancer Progression: A Retrospective Multicenter Comparison of Awake Craniotomy Versus General Anesthesia in High-grade Glioma Resection

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Wishing everyone a very Happy New Year 2023, and welcome to yet another article of the month !. Dr. Benjamin Gruenbaum MD, PhD. is an Assistant Professor in the Neuroanesthesia Division of the Department of Anesthesiology and Perioperative Medicine at the Mayo Clinic, in Jacksonville, Florida. Dr. Gruenbaum is very active in medical student education and neuroscience research, and currently serves on the Education Committee for the Society of Neuroscience in Anesthesiology and Critical Care (SNACC).

As always, we encourage our readers' input on this topic on the SNACC [Twitter](#) feed, or on [Facebook](#).

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In recent years, there has been considerable interest in better understanding how various external factors in the perioperative period might affect the development of metastases and tumor recurrence in patients undergoing surgery for cancer. Although surgical resection of a malignant tumor is often performed with curative intent, many components of the perioperative period are thought to paradoxically promote a tumorigenic environment that facilitates the spread of malignant cells by impacting the inflammatory state of the surgery's microenvironment. Multiple direct and indirect factors have been thought to play a significant role, including the body's physiologic stress response to surgery; inflammation from surgical trauma; and the immune-modulating effects of medications received in the perioperative period, such as commonly-used anesthetics. As the number of cancer surgeries performed globally continues to increase, a better understanding of how these external factors impact long-term clinical outcomes is urgently needed. This issue remains a significant public health concern for patients and clinicians alike.

The potential impact of exposure to different anesthetics on tumor recurrence is rooted in the pre-clinical literature and is thought to reflect differences in the anesthetics' pro-inflammatory effects. This topic gained widespread interest following the landmark paper by Timothy Wigmore et al. in 2016 in *Anesthesiology*,¹ which demonstrated a greater than 50% reduction in mortality when intravenous anesthetics were used compared to volatile anesthetics during cancer surgery. The study, which included more than 10,000 patients, was ultimately limited by its retrospective study design and subsequently generated numerous questions about its relevance to clinical practice. Could the choice of anesthetics used for cancer surgery account for such significant differences in mortality (e.g., is there a causal relationship)? If so, which cancer subtypes and which patients might be most susceptible to these effects of anesthetics? The implications are indeed intriguing. If solid evidence concluded that some anesthetics were more tumorigenic than others, it would undoubtedly be among the most impactful findings in the field of anesthetic research and would have a tremendous impact on the perioperative management of these patients. Numerous studies and clinical trials have subsequently attempted to answer some of these questions. However, the data generated from these recent studies suggest that the impact of anesthetic choice on clinical outcomes following cancer surgery is far from straightforward, and numerous questions still persist.

Of the various cancer sub-types, high-grade gliomas are perhaps among the most exciting and relevant for studying anesthetics' effects on tumor recurrence and survival. Patients with high-grade gliomas commonly undergo surgery with anesthesia because surgical resection is the cornerstone of treatment with curative intent. Moreover, high-grade gliomas are among the most aggressive types of cancer and are associated with a high rate of recurrence and low, 5-year survival rate. However, retrospective studies performed by Grau et al.² and Schmoch et al.³ in 2020 and 2021, respectively, have failed to demonstrate that the choice of anesthetic (e.g., intravenous versus inhalational agents) have a significant impact on recurrence or survival. To date, prospective randomized controlled trials addressing these questions are lacking.

In this month's SNACC Article of the Month, published in the October 2022 issue of the *Journal of Neurosurgical Anesthesiology*, Tumul Chowdhury and colleagues took the question of anesthetic choice a step further by investigating whether performing high-grade glioma resection with awake craniotomy and minimal sedation offered any outcomes benefits over general anesthesia. The study's primary outcome was progression-free survival, and the secondary outcomes included overall survival, postoperative pain scores, and length of hospital stay. The multicenter retrospective cohort study retrospectively evaluated 891 patients; 21% of patients underwent awake craniotomy and 79% general anesthesia. The authors hypothesized that the patients who underwent awake craniotomy would demonstrate outcomes benefit,

including prolonged progression-free survival, less post-operative pain, and shorter hospital stay compared with those who underwent general anesthesia. However, the study failed to demonstrate any outcomes benefit for patients who underwent awake craniotomy or general anesthesia for high-grade glioma resection, suggesting that exposure to commonly-used anesthetics during high-grade glioma resection does not significantly impact long-term outcomes.

The authors of the study correctly point out that their study had several limitations that might account for this lack of differences, including its retrospective design, lack of standardization in anesthesia protocols between patients, lack of randomization to general anesthesia versus awake craniotomy treatment groups, lack of detailed surgical information including surgical technique and extent of tumor resection, and a lack of thorough oncologic follow up. Moreover, the cause of death in these patients was not recorded, and many confounding factors might have impacted the results. Indeed, future randomized controlled trials are needed to address the true impact of awake craniotomy versus general anesthesia on oncologic outcomes in patients undergoing high-grade glioma resection.

Another potentially exciting area for future research would be to assess postoperative fatigue and quality of life in patients undergoing awake craniotomy versus general anesthesia for high-grade glioma resection. Although Chowdhury and colleagues evaluated patients' pre-operative quality of life, they did not reassess this in the postoperative period. The effects of general anesthesia on postoperative fatigue and quality of life cannot be understated, as recent studies in other types of surgeries, including spine surgery,⁴ suggest that these differences might be profound.

References:

1. 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.
2. Grau SJ, Lohr M, Taurisano V, et al. The choice of anaesthesia for glioblastoma surgery does not impact the time to recurrence. *Sci Rep* 2020;10: 5556.
3. Schmoch T, Jungk C, Bruckner T, et al. The anesthetist's choice of inhalational vs. intravenous anesthetics has no impact on survival of glioblastoma patients. *Neurosurg Rev* 2021;44: 2707-2715.
4. De Biase G, Gruenbaum SE, Quinones-Hinojosa A, et al. Spine Surgery Under Spinal vs General Anesthesia: Prospective Analysis of Quality of Life, Fatigue, and Cognition. *Neurosurgery* 2022;90: 186-191.