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The Potential Benefits of Awake Craniotomy for Brain Tumor Resection: An Anesthesiologist's Perspective

Lingzhong Meng, MD, Mitchel S. Berger, MD,† and Adrian W. Gelb, MBChB**

Abstract: Awake craniotomy for brain tumor resection is becoming a standard of care for lesions residing within or in close proximity to regions presumed to have language or sensorimotor function. Evidence shows an improved outcome including greater extent of resection, fewer late neurological deficits, shorter hospital stay, and longer survival after awake brain tumor resection compared with surgery under general anesthesia. The surgeon's ability to maximize tumor resection within the constraint of preserving neurological function by intraoperative stimulation mapping in an awake patient is credited for this advantageous result. It is possible that the care provided by anesthesiologists, especially the avoidance of certain components of general endotracheal anesthesia, may also be important in the outcome of awake brain tumor resection. We present our interpretation of the evidence that we believe substantiates this proposition. However, due to the lack of direct evidence based on randomized-controlled trials and the heterogeneity of anesthetic techniques used for awake craniotomy, our perspective is largely speculative and hypothesis generating that needs to be validated or refuted by future quality research.

Key Words: awake craniotomy, brain tumor resection, beneficial outcome, contribution of anesthesia

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Central nervous system tumors are rare but contribute disproportionately to morbidity and mortality. The average annual age-adjusted incidence of primary central nervous system tumors is about 21 per 100,000 in the United States.[1] Glioma represents about 30% of all and 80% of malignant primary central nervous system tumors.[1,2] Survival is prolonged in glioma patients who undergo resection compared with biopsy alone[3] and the greater the extent of resection the better the outcome.[4] Complete or near-complete surgical removal of low-grade and high-grade gliomas in most locations is generally recommended if possible.[5] However, surgical resection has to be performed within the constraint of preserving the neurological function, especially for tumors that are adjacent to eloquent areas, which is common for gliomas.[6]

It is conventionally called awake craniotomy if the patient is awake at some point of the surgical procedure, mapping, and/or resection. Over decades, awake craniotomy for supratentorial tumor resection has evolved into a standard of care if the lesion is within or in close proximity to regions presumed to have language or sensorimotor function on preoperative imaging.[7–9] The primary goal of awake craniotomy is to maximize the extent of resection while preserving the neurological function by intraoperative stimulation mapping in an awake patient.[4,7–10] As expected, it is primarily used for glioma resection given the incidence, location preference, and infiltrative feature of this type of tumor.

Accumulating evidence shows that awake brain tumor resection is associated with a better outcome. A recent systematic review showed that it led to shorter hospital stay (4 vs. 9 d), fewer neurological deficits (7% vs. 23%), and comparable resection extent and surgery time compared with general anesthesia based on 951 patients from a total of 8 studies.[11] A separate meta-analysis showed that intraoperative stimulation mapping was associated with fewer late severe neurological deficits and greater extent of resection while involving eloquent locations more frequently.[12] However, technical details of anesthesia were not reported, but mapping was presumably done awake as language mapping can be done only in an awake state and sensorimotor mapping, that is, lower stimulation intensity to elicit a response and patient's feedback on subtle reactions, can be done better in an awake patient. Importantly, it was shown that awake brain tumor resection significantly improved survival compared with surgery under general anesthesia for lesions both next to and away from eloquent areas.[10] Other reported benefits associated with awake brain tumor resection include less pain and narcotic usage,[13,14] reduced early postoperative nausea and vomiting,[15] less intraoperative vasopressor use,[13] and satisfactory patients' acceptance.[14,16]

However, awake craniotomy comes with inherent challenges such as desaturation and hypercapnia during

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surgery although these appear to be manageable and usually inconsequential at institutions that do a large volume of awake cases.[9,13,17] Without general anesthesia, the threshold for seizure may be lowered and having a seizure in an awake patient without a secured airway can be an onerous challenge.[18] However, with iced solution irrigation and/or a small propofol bolus, the majority of intraoperative seizures resolve without consequences.[9] In term of the anesthetic regimen, there is no single agent that is superior for every case. Flexibility in selection and dosing of drugs to achieve the most suitable endpoint for patient and surgeon is required.[9]

We speculate that, while the surgeon's ability to perform intraoperative stimulation mapping in an awake patient is crucial,[4,7–12] the anesthesiologist's contribution is also essential. This manuscript discusses our assessment of whether the care provided by anesthesiologists, especially the avoidance of general anesthesia, also contributes to the beneficial outcome of awake brain tumor resection. This is an important topic because it is pertinent to patients' outcome. It is unlikely that different anesthetic techniques contribute equally to the outcome. The question then is if there is one superior technique, what are the important elements or ingredients. Our aim is to substantiate this proposition by discussing the relevant evidence.

ANESTHESIA PRACTICE FOR AWAKE CRANIOTOMY

Before contemplating how anesthesia care contributes to the beneficial outcome associated with awake brain tumor resection, it is imperative to first review the technical details of anesthesia practice for awake craniotomy.

Awake craniotomy for brain tumor resection can be divided into 3 sequential phases—craniotomy, awake mapping before or through tumor resection, and closure. Different anesthetic techniques have been described to cover different phases.[9,13,17,19,20] The technique varies not only interinstitutionally but also interindividually in the same institution. While keeping the patient awake, comfortable and cooperative during the awake phase is not disputed, the anesthetic technique varies from keeping patients awake,[19] keeping patients lightly or deeply sedated,[9,13] to general anesthesia and airway control with either endotracheal tube[20] or laryngeal mask[17] during initial craniotomy and closure. Therefore, even though the anesthesia care of the awake phase is distinctly different to general anesthesia, the opening and closing phases may be similar to general anesthesia depending on the technique being used.

The technical details of the studies comparing awake craniotomy versus general anesthesia for brain tumor resection including the 8 studies identified by the recent systematic review[10,15,21–26] and 1 study that was published afterwards[13] are summarized (Table 1). In these studies, the patients undergoing awake craniotomy did not receive an endotracheal tube or laryngeal mask airway and were kept spontaneously breathing throughout the procedure based on the available data. Moreover, they all had local anesthetic infiltration for pain control and were not exposed to volatile agents except 1 study.[23] None reported sedation status, and interpretation of the awake craniotomy literature would be enhanced by the use of standardized sedation scales, for example, Modified Observer's Assessment of Alertness/sedation, Ramsay Sedation Scale, or one specifically designed for awake craniotomy.

AVOIDANCE OF GENERAL ANESTHESIA-ASSOCIATED PHYSIOLOGICAL DISTURBANCE

Most drugs used during general anesthesia disturb normal physiology in some way. They can affect almost every organ system. Some effects are reversible while some may not be. How these effects affect postoperative outcome is not well established. Factors that may modulate the effects of anesthetic agents include patient's age, physical and medical conditions, and pharmacogenetics,[27] in addition to factors that are as yet unrecognized.

The volatile agents affect every facet of pulmonary physiology.[28] They depress the ventilatory response to hypercapnia and hypoxia. They also affect inspiratory and expiratory muscles, contributing to the reduction of functional residual capacity, formation of atelectasis, and increase in airway resistance. Respiratory rate increases while tidal volume and minute ventilation decreases. Hypoxic pulmonary vasoconstriction is attenuated by most inhaled anesthetics and mucus clearance and surfactant production are also impaired. Propofol, the most commonly used intravenous agent, causes apnea with an induction dose and decrement in tidal volume during infusion. It also depresses the ventilatory responses to hypercapnia and hypoxia and attenuates hypoxic pulmonary vasoconstriction.[29] The use of muscle relaxant during general anesthesia also disturbs the pulmonary physiology by promoting the formation of atelectasis.[30]

Both inhaled and intravenous anesthetics have profound cardioactive and vasoactive properties.[31–36] Volatile agents exert dose-dependent and agent-dependent vasodilatory and negative inotropic effects.[34–36] The newer agents differ from the older ones in that they produce less myocardial depression. Hypotension is frequently encountered during general anesthesia, a consequence of the interaction of mechanical ventilation, myocardial depression, vasodilation, and alterations in both autonomic nervous system activity and baroreceptor reflex control.[33,37–39] Intraoperative hypotension has been linked to various harms including myocardial injury, kidney injury, stroke, and mortality.[40,41] Still, there is no consensus on how to best manage intraoperative hypotension.[42]

Up until recently it was presumed that the effect of general anesthesia on the central nervous system is immediately reversible, that is, an on-and-off phenomenon. However, this belief is now under scrutiny. Accumulating preclinical evidence shows that general anesthetics can contribute to detrimental behavioral outcomes by being

TABLE 1. Anesthetic Techniques Used in Studies Comparing Awake Craniotomy Versus General Anesthesia for Brain Tumor Resection

		Awake Craniotomy			General Anesthesia		
References	Study Design (n, Awake vs. Asleep)	Endotracheal Tube and LMA	Anesthetic Agents	Pain Management	Endotracheal Tube and LMA	Anesthetic Agents	Pain Management
Sacko et al[10]	Prospective (214 vs. 361)	None	Propofol	Local anesthetic infiltration + fentanyl or remifentanil	NA	NA	NA
Gupta et al[21]	Prospective/randomized (26 vs. 27)	None	Propofol	Local anesthetic infiltration + fentanyl	NA	NA	NA
De Benedictis et al[22]	Retrospective (9 vs. 9)	NA	NA	NA	NA	NA	NA
Manninen and Tan[15]	Prospective (50 vs. 57)	None	Midazolam + propofol	Local anesthetic infiltration + fentanyl or remifentanil	Endotracheal tube	Thiopental or propofol + nitrous oxide + isoflurane or desflurane + rocuronium or pancuronium	Fentanyl
Peruzzi et al[23]	Retrospective (20 vs. 19)	None	Propofol + dexmedetomidine + sevoflurane	Local anesthetic infiltration	Endotracheal tube	Propofol + rocuronium or vecuronium + isoflurane or desflurane or sevoflurane	Fentanyl or remifentanil
Ali et al[24]	Prospective (20 vs. 20)	None	Propofol	Local anesthetic infiltration + fentanyl	Endotracheal tube	Propofol + atracurium + isoflurane + nitrous oxide	Fentanyl
Hol et al[25]	Prospective (20 vs. 20)	None	Propofol	Local anesthetic infiltration + remifentanil	Endotracheal tube	Propofol + cisatracurium	Remifentanil
Pinsker et al[26]	Retrospective (52 vs. 27)	NA	NA	NA	NA	NA	NA
Rajan et al[13]	Retrospective (101 vs. 77)	None	Propofol + dexmedetomidine	Local anesthetic infiltration + fentanyl	Endotracheal tube	Propofol + rocuronium + sevoflurane or isoflurane	Fentanyl + remifentanil

LMA indicates laryngeal mask airway; NA, not available.

powerful modulators of neuronal development and thereby function.[43] However, the clinical evidence is fraught with confounders, inadequately powered studies, and firm conclusions remain elusive.[43–45] It has also been suggested that general anesthesia may increase the risk of postoperative cognitive decline,[46] a syndrome associated with increased mortality and negative socioeconomic impact.[47]

General anesthesia also exerts deleterious effects on other organ systems. Inhaled anesthetics can directly cause hepatotoxicity and nephrotoxicity.[48–51] Postoperative nausea and vomiting after general anesthesia is a prevalent major "little problem"[52] where the associated straining may contribute to postoperative cerebral edema or hemorrhage. Thiopental and etomidate can reversibly depress neutrophil chemiluminescence[53] and in addition the latter suppresses adrenal function.[54]

It is an intriguing question to ask if these deleterious effects of general anesthesia on human physiology are attenuated or avoided during awake craniotomy. Volatile agents and muscle relaxants are rarely used during awake craniotomy if the patient is not instrumented by endotracheal tube or laryngeal mask airway. Intravenous agents such as propofol are used in low doses at some institutions.[9] The mainstay of analgesia during awake craniotomy is local anesthetic infiltration supplemented with small doses of opioids if needed. Hypotension is uncommon, especially during the awake phase. The overall dose of vasopressors is much less than that required during general anesthesia.[13] Therefore, depending on the anesthetic technique being used, awake craniotomy may cause less physiological disturbance than general anesthesia, especially if lower doses of drugs are used.

We appreciate that the features and the extent of physiological disturbances are anesthetic agent and especially dose dependent. However, the drugs used for awake brain tumor resection and surgery under general anesthesia overlap. Moreover, the anesthetic depth during the nonawake phases of awake craniotomy may be equivalent to general anesthesia if the patient is heavily sedated, with or without airway instrumentation. Conversely, the anesthetic depth during general anesthesia may not be as deep if adequate analgesia including scalp infiltration is accomplished and the airway is topicalized by local anesthetic spray. Therefore, the heterogeneity of anesthesia practice and the overlap between different techniques make the distinction of the physiological effects between awake craniotomy and general anesthesia difficult.

AVOIDANCE OF MECHANICAL VENTILATION

Patients undergoing awake craniotomy breathe spontaneously when endotracheal tube and laryngeal mask airway are not used. This is radically different to the mechanical ventilation used during general anesthesia.

Mechanical ventilation is not benign. Volutrauma and barotrauma can occur if the tidal volume and airway pressure are high and, conversely, atelectrauma can ensue if the alveoli are derecruited due to low tidal volume and zero positive end-expiratory pressure.[55] Abundant evidence shows that the biophysical insult leads to regional and systemic release of inflammatory mediators that contribute to both lung injury and systemic organ dysfunction.[56–62]

The detrimental effects of large tidal volume ventilation to an already injured lung, especially one with acute respiratory distress syndrome, are well demonstrated.[63] Emerging evidence based on both meta-analysis[64] and randomized-controlled trial[65] shows that positive pressure ventilation using low tidal volume is also associated with a beneficial outcome in patients who have normal lungs.

Therefore, if mechanical ventilation is not used or only used for a short period of time as a temporary measure in patients undergoing awake brain tumor resection, it is a rational assumption that the hazards associated with mechanical ventilation are avoided or reduced.

AVOIDANCE OF GENERAL ANESTHESIA-ASSOCIATED ADVERSE IMPACT ON ANTITUMOR IMMUNITY AND TUMOR PROGRESSION

The primary purpose of surgical resection of any tumor is to cure or debulk the neoplasm. In this regard, the implicit assumption is that surgery is associated with a beneficial outcome. However, mounting evidence suggests that surgery can also incur unfavorable oncological outcomes. This proposition has been elaborated by multiple independent reviews since 2010.[66–74] All of these reviews discussed the adverse impact of anesthesia and analgesia on tumor recurrence and metastasis.

The perception that anesthesia may adversely affect tumor outcome is not novel but somehow escaped scrutiny for years. In 1981, it was shown that malignant pulmonary metastases are enhanced by various anesthetics including thiopental, ketamine, halothane, and nitrous oxide in mice.[75] A few years later, the same group showed in mice that the natural killer (NK) cell activity is decreased by halothane and ketamine but not thiopental and nitrous oxide.[76] A separate investigative group later showed that ketamine, thiopental, and halothane, but not propofol, suppresses NK-cell activity and promotes tumor retention and metastases in rats.[77]

Among anesthetic agents, propofol presents favorable properties for tumor surgery. It does not suppress NK-cell activity.[77] It inhibits cyclooxygenase activity[78] and suppresses prostaglandin E2 production.[78,79] It favorably maintains peripheral helper T lymphocytes ratio (T helper 1 to T helper 2) in patients undergoing craniotomy for both tumor resection and aneurysm clipping.[80] Therefore, propofol may enhance antitumor immunity.[81,82] Propofol also has anti-inflammatory and antioxidant properties.[83] In addition, propofol inhibits the activation of hypoxia-inducible factor-1α in prostate cancer cells, a property being evaluated for antitumor effect.[68,84] In contrast, halothane suppresses NK-cell activity[77] and isoflurane adversely affects peripheral helper T lymphocytes ratio after craniotomy[80] and induces up-regulation of hypoxia-inducible factor-1α.[84] Therefore, inhaled anesthetics are discouraged by some authors for tumor surgery.[68,85]

Pain control is a top priority in tumor patients and opioids are widely used for both acute surgical pain and chronic cancer-related pain. However, the commonly used opioids including morphine and fentanyl decrease cellular and humoral immunity, increase tumor angiogenesis while decreasing tumor cell apoptosis.[73] The adjunct analgesics including ketamine, clonidine, and dexmedetomidine may directly stimulate cancer cells and increase metastases.[73] In view of the fact that poorly controlled cancer pain, likely via beta-adrenergic stimulation,[86] promotes tumor growth and metastasis,[67,73] pain management in tumor patients remains challenging.

Local anesthetics, in contrast, can directly inhibit tumor growth even though this effect seems agent specific.[73] The mechanism may relate to the blockade of voltage-gated sodium channels.[70] Regional anesthesia using local anesthetics spares the systemic usage of opioids. Multiple independent systematic reviews on the use of regional anesthesia in tumor patients have been performed and found it beneficial[66,69,71,73,74] but none of these had specifically examined the effect of regional anesthesia in patients with brain tumors. Overall, regional anesthesia or analgesia seems to have a beneficial effect on tumor outcome based on largely retrospective cohort studies. However, due to the lack of meaningful prospective randomized and controlled trials, recommendations for clinical care cannot yet be developed.

In light of this evidence, even though largely based on nonbrain tumor studies, it is rational to speculate that avoiding the adverse impact on antitumor immunity and tumor progression associated with general anesthesia may contribute to the beneficial outcome after awake brain tumor resection if the anesthesia primarily relies on propofol and local anesthetics. However, real-world clinical practice is more complicated because the anesthetic techniques being used for awake craniotomy are heterogenous and can overlap with general anesthesia. For example, propofol or total intravenous anesthesia and local anesthetic infiltration are used for brain tumor resection under general anesthesia at some institutions as well and dexmedetomidine, even though it may promote tumor metastasis, has been used for awake brain tumor resection, too. Moreover, how the tumor behavior is affected by the drug dose, low versus high and none versus low, is unknown. Therefore, this salient topic pertinent to the oncological effect of anesthetic and analgesic techniques in patients undergoing brain tumor surgery remains unsettled. The importance of this topic is highlighted by the recent special issue of the British Journal of Anaesthesia on "Anesthesia and Cancer" contributed to by a multinational group of experts. However, their consensus was that they were not able to draw a conclusion on the effect of anesthetic and analgesic techniques on cancer outcome due to the lack of randomized-controlled trials.[87]

FURTHER CONSIDERATIONS

The decision to perform awake craniotomy versus general anesthesia for brain tumor resection takes into account the patient's age, body size, physical condition, medical comorbidity, neurological status, motivation, and airway patency in addition to the tumor location. Patient selection is both institution and surgeon dependent and constitutes a source of bias during the comparison of outcomes with general anesthesia. Therefore, it would be preferable if the benefits of awake brain tumor resection could be confirmed by randomized-controlled trials. Unfortunately, randomization into groups of awake craniotomy versus general anesthesia for brain tumors that are adjacent to eloquent areas is deemed unethical because awake craniotomy is the standard of care per experts' opinion.[9] The only randomized-controlled trial that was published in 2007 was underpowered because only 26 and 27 patients were recruited in the awake craniotomy and general anesthesia groups, respectively.[21]

Because of the heterogeneity of anesthetic techniques being used for awake craniotomy and the overlap of anesthetic techniques used for awake craniotomy and general anesthesia, it is difficult to ascribe a specific component of anesthesia as the cause of the benefit associated with awake brain tumor resection or the relative detrimental effect of general anesthesia. This shortfall, due to the absence of randomized trials, calls for efforts to establish anesthesia expert recommendations for awake craniotomy, at a minimum. Tumors in noneloquent areas may be a potential target for ethical comparisons of outcomes by anesthetic technique and would allow for stronger evidence than expert opinion.

If awake brain tumor resection is truly beneficial, it has to have its roots in either the surgical technique or the anesthetic technique. However, this should not ignore another factor that is the greater attention devoted by both the surgeon and anesthesiologist to the patient. Awake craniotomy drives anesthesiologists to be more attentive to details in preoperative preparation, patient communication, anxiolysis, analgesia, antiemesis, optimal patient positioning, and fluid balance. Attention to these details should be a component of general anesthesia as well. However, direct continual feedback from the patient about positioning, analgesia needs, feeling "dry," etc. is not obtained until the operation is completed. In addition, direct and congenial interaction between an awake patient and the care team during awake craniotomy is a unique process that does not exist under general anesthesia. Whether this process itself and/or the information gained from this process also contribute to outcomes remain to be determined.

Overall, direct and quality evidence pertinent to the role the anesthesia plays in the outcome after awake brain tumor resection is lacking. Most studies referenced by this manuscript were not performed in patients undergoing brain tumor resection. Therefore, our perspective should be regarded as speculative and hypothesis generating only. Our views need to be validated or refuted by future well-designed and well-executed research.

SUMMARY

Awake craniotomy for brain tumor resection is becoming a standard of care for lesions residing within or in close proximity to regions presumed to have language or sensorimotor function based on preoperative imaging. Evidence, largely based on trials that were not randomized and controlled, showed that awake brain tumor resection is associated with an improved outcome compared with surgery performed under general anesthesia. The surgeon's ability to conduct intraoperative cortical and subcortical mapping in an awake patient accounts for, but is unlikely to be the exclusive cause of, the favorable result. There is a speculation that the care provided by anesthesiologists, especially the avoidance of certain components of general endotracheal anesthesia, may also be important in the outcome of awake craniotomy for brain tumor resection. Differences in the anesthetic methods used in craniotomy with intraoperative monitoring of an awake patient may be a reason for the speculated superiority. Outcome-oriented clinical care should be embraced. Understanding the mechanisms of the favorable outcome can facilitate the continuous improvement of the patient's quality of care.

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