Management of anesthesia in awake craniotomy

F. PICCIONI [1], M. FANZIO [2]

[1]Department of Anesthesiology and Intensive Care, IRCCS Foundation, National Cancer Institute, Milan, Italy; [2]Second Department of Anesthesiology and Intensive Care, IRCCS Foundation, "S. Matteo" Hospital, Pavia, Italy

ABSTRACT

The awake craniotomy technique was originally introduced for the surgical treatment of epilepsy and has subsequently been used in patients undergoing surgical management of supratentorial tumors, arteriovenous malformation, deep brain stimulation, and mycotic aneurysms near critical brain regions. This surgical approach aims to maximize lesion resection while sparing important areas of the brain (motor, somatosensory, and language areas). Awake craniotomy offers great advantages with respect to patient outcome. In this type of procedure, the anesthetist's goal is to make the operation safe and effective and reduce the psychophysical distress of the patient. Many authors have described different anesthetic care protocols for awake craniotomy based on monitored or general anesthesia; however, there is still no consensus as to the best anesthetic technique. The most commonly used drugs for awake craniotomies are propofol and remifentanil, but dexmedetomidine is beginning to be used more commonly outside of Europe. Personal experience, careful planning, and attention to detail are the basis for obtaining good awake craniotomy results. Additional studies are necessary in order to optimize the procedure, reduce complications, and improve patient tolerance. The aim of this review is to present a thorough report of the literature, with particular attention to neuro-oncology surgery

Key words: Craniotomy - Anesthesia - Brain neoplasms - Brain mapping - Propofol - Remifentanil - Dexmedetomidine.

The awake craniotomy technique was introduced for surgical treatment of epilepsy, and has subsequently been used in patients undergoing surgical management of supratentorial tumors, arteriovenous malformation, deep brain stimulation, and mycotic aneurysms near critical regions of the brain.[1-3] This approach aims to maximize lesion resection while sparing important foci such as the motor, somatosensory and language areas. During this surgical technique, active participation by the patient is necessary to facilitate cortical mapping. Electrocorticography (ECoG) and patient response to electrical stimulation of the cerebral cortex guide the surgeon's intraoperative decisions. As mentioned, awake craniotomy was originally introduced for the treatment of intractable epilepsy at the beginning of the 20th century. During the last three decades, this technique has been used more frequently in patients undergoing surgery for brain tumor resections in close proximity to critical neurologic areas. The main goal in neurosurgery is to obtain an accurate excision of the lesion while preventing functional disabilities in order to achieve a better prognosis and improve quality of life for the patient. In regards to neuro-oncology surgery, awake craniotomy offers the unique possibility of reducing postoperative morbidity, thus facilitating early discharge from the hospital.[4-8] Anesthetic care is probably the most unique aspect of awake craniotomy. The primary goal of the anesthetist is to make the operation safe and effective while reducing the psychophysical distress of the patient. Many authors have described different protocols for anesthetic care during awake craniotomy based on monitored anesthesia care (MAC) or general anesthesia (the so called asleep-awake-asleep technique [AAA]). The aim of this paper is to present a thor-

TABLE I.— *Observer's Assessment of Alertness/Sedation Scale.*[20]

OAA/S	Answering	Vocal expression	Facial expression	Eyes	Level of sedation
5	Ready to calling	Normal	Normal	Normal	Awake
4	Slow to calling	Initial slowing	Medium relaxing	Medium relaxing	Light
3	Only to loud calling	Slowing	Slowing	Marked ptosis	Moderate
2	Only to shakes	Incomprehensible words	—	—	Deep
1	—	—	—	—	General anesthesia

OAA/S: Observer's Assessment of Alertness/Sedation Scale.

ough literature review of awake craniotomy, with particular attention to neuro-oncology surgery.

Historic Development of Awake Anesthesia

Horsley first undertook awake craniotomies using local anesthesia in 1886.[9] By 1934, Davidoff began to combine local anesthesia and sedation, while Penfield preferred sedation only following electric stimulation testing.[9] In the 1950s, Pasquet employed general anesthesia after testing with local anesthesia (he defined this technique as "vocal anesthesia").[9] The first important change in the standard of anesthetic care for awake craniotomy is dated back to 1959, when De Castro and Mundeleer introduced the concept of neuroleptoanesthesia, based on haloperidol and phenoperidine administration.[10] Since this discovery, different combinations of neuroleptics and opioids have been used, and one of these, Innovar (droperidol with fentanyl), was specifically marketed for use in neuroleptoanesthesia. This pharmacologic regimen was the standard for awake craniotomies for over 30 years. In 1988, Archer described his studies with 354 awake craniotomies for cortical resection of epilepsy using local anesthesia and intravenous fentanyl and droperidol.[11] The following year, Welling described a similar technique replacing fentanyl with alfentanil.[12] Four years later, Silbergeld published the first data using propofol sedation in awake craniotomy.[13] Silbergeld's work is largely considered to be the second great change to the field of awake craniotomy. Since this discovery, propofol infusion has became popular during awake craniotomies for its rapid onset, titrability, and short recovery time. In recent years, many studies have examined this type of anesthetic care, comparing neuroleptoanalgesia to propofol and fentanyl-based sedation.[14] The studies have largely focused on propofol sedation in combination with different opioids,[15, 16] in addition to examining many technical aspects of the procedure (laryngeal mask airway [LMA],[17] Bispectral Index [BIS],[18] target-controlled infusion [TCI][18]).

Despite multiple different anesthetic strategies, modern anesthetic approaches may be generally divided as follows: MAC [19] and AAA. Since this classification is not standardized in international literature, more absolute definitions for these techniques have been proposed.

MAC: the patient is sedated, can breath spontaneously, and is responsive to name calling (assessment of sedation is using the Observer's Assessment of Alertness/Sedation Scale [OAA/S] score ≥3 [20] [Table I] or BIS score >60). Oxygen administration and airway control are obtained using devices that allow partial or no mechanical ventilation.

AAA: this technique is comprised of deep sedation or general anesthesia, and spontaneous breathing is possible (OAA/S score <3 [20] [Table I] or BIS score <60). Oxygen administration and airway control are obtained with devices that allow for mechanical ventilation. The patient is awakened (and usually extubated) throughout the procedure as needed (for example, for brain mapping and/or tumor resection).

Each of these anesthesia care techniques is examined in detail in dedicated paragraphs.

Anesthetic aims

Each different anesthetic technique has specific aims.[21, 22]

1. Maintaining patient cooperation:
— optimal analgesic care;

— adequate sedation and anxiolysis during the different surgical steps;
— comfortable positioning;
— nausea, vomiting, and seizure prevention.

2. Homeostasis:
— safe airways and adequate ventilation;
— hemodynamic stability;
— normal intracranial pressure.

3. Most important for epilepsy surgery:
— limited interference with electrophysiological recordings.

Throughout these procedures, it is extremely important to remember that sedatives and opioids may interfere with electrophysiological intraoperative recordings. Neuroleptic and propofol administration must be discontinued prior to cortical mapping in order to obtain an accurate evaluation of the ECoG recordings and to avoid suppression of interictal spike activity.[23] Opioids are particularly effective in selectively activating interictal epileptiform activity. Such opioid-induced activation may assist the surgeon in selecting an appropriate resection location during epilepsy surgery,[24] but this activation is a negative interference during tumor surgery. Opioids may also promote signs of neuroexcitation such as nystagmus, muscle rigidity, myoclonus, and seizure-like activity.[24] However, at low doses (0.1 μg/kg/min), remifentanil, a short-acting opioid, does not adversely affect ECoG recordings even during the awake part of the procedure.[25]

Successful achievement of the abovementioned aims ensures optimal conditions for both the surgeon as well as the patient. Achievement of these aims results in precise and standardized anesthetic care based on the individual patient's characteristics, the anesthetist's experience, and available technical devices.

Preoperative evaluation

Preoperative evaluation is necessary in order to evaluate the patient's health, cooperation, and airway characteristics. The neurosurgeon must explain the advantages, necessity, and nature of the procedure. In regards to tumor surgery, the most common pathological diagnosis in patients undergoing awake craniotomy is low-grade glioma, however, high-grade gliomas, metastases to the brain, and meningiomas near functional cortex resection are also frequently planned as awake craniotomies.[7, 26-29] Preoperative evaluation must encompass a complete clinical examination. In planning a preoperative evaluation, it is useful to follow the instructions and guidelines of specific societies such as the Italian Society of Analgesia Anesthesia and Intensive Care,[30] or the American Society of Anesthesiologists (ASA).[31] A specific and focused clinical evaluation is extremely important, as underlined by Bonhomme *et al.* [21] Preoperative evaluation must consider the following aspects.

1. Upper airways:
— prediction of difficult tracheal intubation (physical conformation and past intubation);
— obstructive apnea risk (obesity, sleep apnea, retrognathia).

2. Epilepsy:
— pharmacotherapy;
— antiepileptic drug serum concentration;
— type and frequency of seizures.

3. Nausea and vomiting:
— past anesthesia;
— kinetosis.

4. Intracranial pressure estimation:
— type of lesion;
— radiological and clinical signs.

5. Hemorrhagic risk:
— type and localization of lesion;
— therapy (antiplatelet drugs);
— medical history.

6. Patient cooperation:
— anxiety;
— pain tolerance;
— neurological deficits.

Preoperative airway evaluation is essential given the difficulty of managing airway complications during the procedure. Sleep apnea syndrome must be considered as an absolute exclusion criterion.[28] Evaluation of brain swelling is also important, since it is much more difficult to control intracranial pressure during spontaneous breathing as compared to mechanical ventilation. Epileptic patients must also be closely evaluated because uncontrollable seizures are relative exclusion criteria for awake craniotomy.[28] The occurrence of intraoperative stimulation-associated seizures may be related to low antiepileptic drug

serum concentrations, stimulation technique,[32] and anesthesia regimen (high-dose opioids and neuroleptics). Interestingly, according to Szelényi, patients with symptomatic epilepsy do not appear to have a higher risk of intraoperative stimulation-associated seizures than patients without symptomatic epilepsy during awake tumor resection.[32] Finally, the patient's complete cooperation and participation are critically necessary for the procedure. Profound dysphasia and confusion are absolute exclusion criteria.[5, 28] In regards to patient selection and intraoperative strategy, in 2006 Picht *et al.* proposed an interesting multimodal protocol for awake craniotomy in language cortex tumor surgery: following cortical mapping, the procedure is continued under MAC or general anesthesia according to the clinical status of the patient and the combined outcomes of brain mapping and functional magnetic resonance imaging (fMRI).[28]

Prior to surgery, the patient must be informed about potential risks, safety measures, stages of the procedure, and what will occur while he/she is in the operating room. The anesthetist must not conceal sounds (monitor alarms, cranial drilling, elektroknife, ultrasonic surgical aspirator) or discomforts (unchangeable position, aphasia during cortical mapping) from the patient, and the patient must understand that these discomforts are necessary to the procedure. A visit to the operating room before surgery is a good idea in order to familiarize the patient with the sounds and equipment in the rooms. The anesthetist must gain the patient's confidence, as the patient will depend on him during the procedure.

Operating room organization

Common anesthesia equipment includes airway devices, local anesthetics, sedative drugs, and other medications reserved for adverse events (antiemetics, vasopressors, anticonvulsants, cold solution). The operating room temperature must be suitable; the surgical table must be covered with soft, thick dressing, and the surgical team must be instructed to speak and move only if necessary. It is important to study the position of the instruments in order to minimize unnecessary movements of objects and personnel. Moreover, the patient's face must be in a position that allows him to look at the anesthetist and at pictures during brain mapping, but must also be accessible for airway treatment during emergencies. An audio-video recorder system should be used so that the surgeon can see and hear the patient's responses during cortical mapping.[22]

Premedication

There is no general consensus regarding premedication, and decisions should be made based on the patient's clinical condition, the anesthetist's opinion, and hospital standards. Some authors do not administer any premedication.[8, 14, 15, 33] Midazolam is the most frequently used benzodiazepine for awake craniotomies:[8, 34-40] it is a short-acting, rapid-onset drug which is twice as effective as diazepam. Midazolam is sometimes combined with opioids such as fentanyl,[41] but this may increase the respiratory depressive effects of each drug. Some authors prefer to use other benzodiazepines such as alprazolam.[18] Benzodiazepines may have some negative effects during awake craniotomy such respiratory depression, paradox agitation or delirium, and interference with electrocorticographic recording. Given these potential complications, midazolam is the best benzodiazepine for awake craniotomies because of its short-acting effect. Recently, Schulz has discouraged benzodiazepine administration before awake craniotomy because these types of drugs may reduce pharynx muscular tone, influence cognitive function, and minimize epileptic foci.[42] Clonidine is a good alternative to benzodiazepines: several studies have proved it to be safe for oral administration.[43] Furthermore, clonidine has been shown to be efficacious in neurosurgery when it is necessary to control the hemodynamic response to tracheal intubation, and in application of the Mayfield headholder.[44] In some centers, clonidine is administered at a dose of 2-3 μg/kg orally one hour before arrival to the operating room.[42, 45] Anticholinergic administration is debatable because its antisalivation effect may be troublesome for awake patients. Moreover, patients are permitted to wet their lips with water during surgery. Using the MAC protocol, atropine is rarely administered[18, 39] but is commonly used before induction with the AAA protocol.[46, 47] Antiemetic prophylaxis is desirable as a precaution-

ary measure. Opioid administration and *dura mater* or cerebral vessels traction may induce intractable nausea and vomiting.[14, 42] Vomiting is extremely dangerous during surgery due to risk of aspiration, rise in intracranial pressure, and patient agitation and movement. Propofol administration is undoubtedly useful to prevent perioperative nausea and vomiting.[48] The majority of antiemetics contain metoclopramide (10 mg) [37, 40] and ondansetron (4-8 mg).[14, 33, 39, 40, 49] Low doses of droperidol (0.625-2.5 mg) [7, 39] and dexamethasone (4-16 mg) [39, 42] are also used. Many authors administer ranitidine for gastric protection and, combined with antiemetics, for reducing the risk of *ab ingestis* pneumonia if vomiting should occur.[37, 39-42, 49] Additional medications are also administered before surgery, even if they are non-specific premedication drugs. Usually patients are given antibiotics and anticonvulsants before or at the beginning of the procedure. Many authors administer preoperative non-steroidal anti-inflammatory drugs such as diclofenac[33] or acetaminophen,[33, 37, 42] opioids such as fentanyl, [35, 37, 40] and dexamethasone.[42, 45]

Local anesthesia

Anesthetic care always includes scalp block. The local anesthetic must assure an eight-hour duration of block. A 40 to 60 mL anesthetic volume is used for infiltration. High local anesthetic volume and well-vascularized areas may predispose to anesthetic toxicity. The use of adrenaline (5 μg/mL, 1:200 000 dilution) both minimizes acute rises in plasma anesthetic concentration and maximizes the duration of the block. Clinical vigilance is particularly indicated within 15 minutes after scalp block.[50, 51] With regards to toxicity, ropivacaine and levobupivacaine appear to be safer than bupivacaine.[52] Despite this difference, bupivacaine is the most commonly used local anesthetic in the literature. Archer in 1988 [11] is the only author to report clinical cases related to local anesthetic toxicity during awake craniotomy.

Local anesthetic blocks are performed to include six nerves [22, 53-55] (Figure 1):

1. auriculotemporal nerve (mandibular branch of trigeminal nerve): infiltration over zygomatic process and distal temporal artery;

2. zygomaticotemporal nerve (zygomatic nerve's terminal root that originates from maxillary branch of trigeminal nerve): infiltration from supraorbital margin to posterior part of zygomatic arch; deep and superficial injections are recommended since the area above the temporalis fascia is the most frequently reported site of postoperative pain;

3. supraorbital nerve (root of frontal nerve which originates from ophthalmic branch of trigeminal nerve): infiltration from the nasal root to the midpoint of the eye;

4. supratrochlear nerve (root of frontal nerve which originates from ophthalmic branch of trigeminal nerve): infiltration together with supraorbital nerve;

5. greater occipital nerve (posterior ramus of C2): infiltration about 2.5 cm lateral to the nuchal's median line, directly medial to occipital artery;

6. lesser occipital nerve (anterior branches of C2 and C3): infiltration 2.5 cm lateral to greater occipital nerve one.

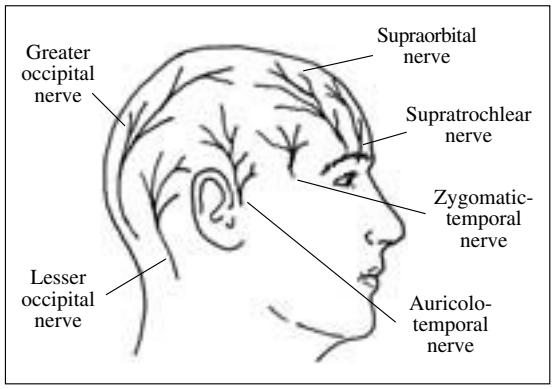

Figure 1.—Innervation of the scalp.

These nerve blocks are usually performed on the surgical scalp side, however, Costello suggests including the six nerves on both sides and to avoid ring blockade of the scalp that requires a larger volume of local anesthetic.[22] On occasion, local anesthesia may be completed using a superficial cervical plexus block.[21] Additional infiltration is usually performed at the three head holder pin sites and along the skin incision line.

Finally, in 2000, Gebhard described the case of a man with involuntary spontaneous jerking of his right upper and lower extremities who underwent an awake craniotomy for intractable seizures. Complete control of movement was a prerequi-

TABLE II.— *Intraoperative complication incidence in different studies related to anesthetic management.*

Year	Author	Reference	Airway obstruction	Desaturation/hypoxia	Hypertension	Hypotension
MAC						
1988	Archer[a]	11	nr	nr	nr	nr
1993	Gignac[b]	15	nr	0/20/10	nr	nr
1997	Herrick[c]	14	5/0	nr	nr	nr
1998	Danks[d]	35	0/0	nr	0/0	nr
2000	Danks[e]	27	nr	nr	23	nr
2001	Blanshard[f]	5	0.4	nr	nr	0.8
2001	Berkenstadt[g]	45	4	28	4	0
2002	Manninen[h]	7	nr	nr	nr	nr
2005	Keifer[i]	37	nr	nr	nr	0
2006	Picht[j]	28	0	28	nr	nr
2006	Manninen[k]	8	20/12	4/0	4/0	0/8
2006	Skucas[l]	62	2	2	11	56
AAA						
1998	Huncke[m]	65	0	nr	nr	nr
2003	Sarang[n]	33	7/0/0	nr	0/11/0	0/6/21
2004	Audu[o]	38	15	nr	nr	nr
DEX						
2005	Ard[p]	66	0	0	24	18

Values expressed in %; MAC: monitored anesthesia care; AAA: awake-asleep-awake technique; DEX: dexmedetomidine; nr: not reported; LA: local anesthetic; GA: general anesthesia; *Awake craniotomy for intractable seizures studies. ° This value was calculated over 16 patients (for 9 cases conversion to GA was related to surgical protocol). [a] 354 pts; retrospective study; droperidol + fentanyl. [b] 30 pts; perspective study; droperidol + fentanyl vs alfentanil vs sufentanil. [c] 37 pts; perspective study; PCS propofol vs droperidol + fentanyl. [d] 21 pts; perspective study; midazolam + sufentanil + fentanyl vs propofol + midazolam + sufentanil + fentanyl. [e] 157 pts; retrospective study; comparison as "d" study. [f] 241 pts; retrospective study; midazolam o propofol + fentanyl o remifentanil. [g] 25 pts; perspective study; propofol + remifentanil + clonidine. [h] 107 pts; perspective study; midazolam + fentanyl or remifentanil ± propofol. [i] 98 pts; retrospective study; propofol + remifentanil. [j] 25 pts; perspective study; propofol + remifentanil. [k] 50 pts; perspective study; propofol + remifentanil vs propofol + fentanyl. [l] 332 pts; retrospective study; propofol. [m] 10 pts; perspective study; N_2O ± sevoflurane ± desflurane ± isoflurano ± propofol. [n] 99 pts; retrospective study; MAC: propofol + fentanyl ± midazolam ± droperidol vs AAA: propofol + fentanyl vs AAA: propofol + remifentanil. [o] 20 pts; perspective study; propofol. [pa] 17 pts; perspective study; dexmedetomidine + sevoflurane + N_2O ± remifentanil.

site for surgery. An interscalene block, musculocutaneous and ulnar nerve block, and continuous femoral nerve block were performed in order to prevent movement. This was the first reported case using regional anesthesia during an awake craniotomy.[36]

Monitored anesthesia care

According to the ASA, MAC is a specific anesthetic protocol that includes careful monitoring and support of vital functions. The anesthetist administers sedatives, analgesics, and hypnotics, addresses any clinical problems, and provides the patient with psychological support during diagnostic and therapeutic procedures. The ASA recommends that the provider of MAC must be prepared and qualified to convert to general anesthesia if necessary.[56] With regards to awake craniotomy, this type of anesthetic care has developed from the logic evolution of pioneering experiences using neuroleptoanalgesia. The introduction of clinical propofol use has favored this evolution by allowing for better patient management.[13, 14] After Silbergeld's publication,[13] Gignac in 1993 compared droperidol administerion combined with fentanyl, alfentanil, or sufentanil in 30 patients.[15] The conclusion of this study was that there was no difference between fentanyl and newer opioids in awake craniotomy. Four years later, Herrick proposed patient-controlled sedation (PCS) with propofol as a valid alternative to neuroleptoanalgesia.[14] Since that time, the neuroleptoanalgesia era could be considered finished in the field of awake craniotomy. The diffusion of new short-acting drugs such as propofol and remifentanil has simplified sedation and allows for rapid awakening in 5-20 minutes. Despite rapid and complete diffusion of propofol, Danks has determined that propofol use is less safe when compared to

Tachycardia	Bradycardia	Seizures	Nausea	Poor cooperation	Brain swelling	LA toxicity	Conversion to GA
nr	nr	16*	8	2	1	2	0
nr	nr	10/30/10*	50/30/70	20/0/10	nr	nr	0
10/35	nr	0/41*	10/18	nr	nr	nr	5/11
nr	nr	0/20	nr	nr	0/0	nr	nr
nr	nr	7.6*	0.6	7	2.5	nr	0.6
nr	nr	8	6.6	nr	0	nr	nr
0	0	8	0	4	0	nr	4
nr	nr	nr	0	nr	nr	nr	nr
nr	nr	3*	8	7	nr	0	0
nr	nr	32	nr	20	8	nr	6.2°
nr	nr	0/16	0/0	16/8	4/4	nr	0/0
14	0.3	3*	0.9	1.5	0.6	0	0
nr	nr	0*	0	0	0	nr	0
nr	nr	0/6/0		0/3/5	nr	0/0/0	0
nr	nr	nr*	nr	nr	nr	nr	0
0	0	6*	6	12	0	0	0

midazolam combined with opioids in two different studies.[27, 35] Since this study, all awake craniotomy published protocols have included propofol administration except Manninen's study[7] in 2002 (optional propofol infusion) and some dexmedetomidine regimens.[57, 58] Today, propofol is widely employed for neurosurgical anesthesia (and awake craniotomy) because of its easily titratable sedative effect and rapid recovery with clear-headedness.[59] Propofol decreases cerebral oxygen consumption, reduces intracranial pressure, and has potent anti-convulsant properties.[60] Propofol also has antiemetic properties and may be administered using a TCI technique.[16, 18, 33, 39] TCI allows for good drug titration, allowing the anesthetist to predict arousal after long-term infusions and avoid oversedation. Normally, propofol TIVA infusion is set to 2-3 mg/kg/h; however, using a TCI protocol the propofol effect-site concentration (C_e) ranges between 1-2 μg/mL. Furthermore, the use of propofol sedation does not appear to interfere with ECoG if infusion is stopped 15 minutes before recording according to Herrick,[23] and 20 minutes in pediatric settings according to Soriano.[61] Some authors employ propofol sedation only in combination with local anesthesia and without opioids infusion and are able to achieve good pain control.[33, 62] In recent years, most anesthetists have replaced fentanyl with low-dose remifentanil (0.05-0.1 μg/kg/min, C_e=1-3 ng/mL if a TCI protocol is used). Remifentanil is a clinically versatile opioid and is useful for intravenous analgesia and sedation in spontaneously breathing patients. Remifentanil has favorable pharmacokinetic properties and is minimally altered by extremes of age or renal or hepatic dysfunction. These properties enable easy titration and rapid dissipation of the clinical effects of this agent. In fact, remifentanil's context-sensitive half-life is very short even after prolonged infusion.[63] According to Herrick, this short-acting opioid at a low-dose infusion (0.1 μg/kg/min) appears to not interfere with ECoG, although additional specific studies on this effect are needed.[25] Commonly, both propofol and opioid infusion are discontinued about 15 minutes before brain mapping and are resumed at the beginning of closure of the *dura*. In the MAC protocol, the first aim is to ensure adequate spontaneous ventilation. During this anesthetic technique, airway management is minimal and non-invasive, as indicated by prior definition. In most centers, patients receive supplemental oxygen via nasal prongs or facial mask. Nasopharynx cannula may be a good alternative choice.[37, 39] This airway device is rarely used because of the risk of nose bleeding, however, once

positioned correctly it is well-tolerated and allows ventilation support if a mechanical ventilator is connected and mouth and opposite nostril closed.[64] Airway obstruction occurs with variable but not negligible frequency (0-20%), leading to oxygen desaturation and hypoxic episodes (0-20%) (Table II). Adequate clinical vigilance concerning respiratory function is necessary throughout the procedure.

Asleep-awake-asleep technique

This anesthetic approach consists of general anesthesia before and after brain mapping. In the 1950s, Penfield described blind nasotracheal intubation after cortical mapping.[67] Meanwhile, Hall[68] and Ingvar,[69] used nasotracheal intubation to maintain the tracheal tube during craniotomy for intractable epilepsy. Hall administered succinilcholine as continuous infusion to obtain generalized muscle relaxation, and Ingvar administered a local anesthetic in the airways through a fine catheter with small holes (but none of these patients could speak during brain mapping!). In 1993, Weiss placed a tracheal tube in one nostril at 22 cm in order to support ventilation during propofol administration with N_2O general anesthesia.[34] In 1998, Huncke *et al.* gave great force to the AAA technique for epilepsy surgery.[65] They described their experience with 10 patients who, after local anesthesia, were awake intubated with a fiberoptic laryngoscope at the beginning of the procedure and again after cortical mapping (two orotracheal intubations and eight nasotracheal intubations). The tracheal tube was modified by attaching a fine catheter with multiple holes for topic delivery of local anesthetic. The described technique, although complex, was considered to be safe with respect to airway and CO_2 control. Over the following years, this article became a landmark publication for many authors who proposed similar anesthetic approaches which described use of a laryngeal mask instead of a tracheal tube. In recent years, LMA has been widely used for awake craniotomy with patients under spontaneous breathing protocols. These patients are supported with mechanical ventilation only if necessary.[33, 41, 66, 70, 71] Other anesthetists have preferred mechanical ventilation with LMA with or without myoresolution.[17, 47, 49] Shinokuma described a case in which the laryngeal mask was left in place throughout the procedure with clear and comprehensible phonation.[72] Finally, others use LMA only during the first part of surgery and finish the craniotomy by performing MAC sedation (this technique has been named asleep-awake).[47, 49, 73] Even if LMA cannot ensure the same airway protection as a tracheal tube, it has renewed great interest in this type of surgery because it is a recent, accessible, and well-known device. Different techniques of LMA positioning have been widely described[74] in awake patients[41, 75, 76] and in both lateral and semi-sitting positions.[77, 78] The AAA technique has been successfully performed using a cuffed oropharyngeal airway (COPA),[38]nasal mask with BiPAP©, or proportional-assist ventilation support.[46] In a recent article, Schulz suggested placing a nasotracheal tube with the tip above the rima glottidis throughout the procedure. With this positioning, if necessary the tracheal tube may be advanced into the trachea under fiberoptic guidance.[42] Finally, Gonzales has recently described the use of two nasopharynx cannulas combined with pressure support ventilation in an obese patient.[79] Given this information, there appears to be a large number of airway control options when performing AAA, but LMA seems to be the most widely accepted technique by most authors. Laryngeal mask airway approaches offer significant advantages over tracheal tube approaches, including avoidance of the laryngoscope and the need for head extension, easier placement in difficult patient position, and reduced incidence of coughing and gagging during emergence. ProSeal LMA may be a better choice than classic LMA because it incorporates a second tube that permits blind insertion of a gastric tube, thus reducing risks of gastric insufflation and pulmonary aspiration.

The AAA technique is mostly commonly performed by administering propofol and remifentanil in combination. Propofol, compared with volatile anesthesia, increases cerebral perfusion pressure, decreases neurophysiologic monitoring interference, appears to ensure neuroprotection, and decreases the incidence of nausea and vomiting.[59] In conclusion, the AAA technique offers, undoubtedly, the advantages of good airway control and adequate deep sedation, and the patient does not suffer from pain or discomfort. Nevertheless, this anes-

thetic approach is more complex than MAC, particularly when repositioning of an airway device is necessary for closure (while the patient is often in the lateral position with his/her head fixed to the Mayfield head holder).

Intraoperative monitoring

Intraoperative monitoring typically includes electrocardiogram, invasive and non-invasive blood pressure measurements, pulse oximetry (SpO_2), respiratory rate, capnography ($EtCO_2$), and body temperature. Normally, a urinary catheter is also inserted. If large blood losses are expected, a central venous catheter is positioned.[7] Invasive blood pressure monitoring is not used in all centers,[7, 8, 14, 27, 35, 62] but is considered necessary in order to carefully evaluate arterial pressure changes, $PaCO_2$ and other useful parameters such as hemoglobin, glucose, and plasma electrolytes. $EtCO_2$ is measured via different devices involved in the anesthetic technique: nasopharyngeal cannula,[33, 39] nasal prongs,[5, 7, 8, 14, 25, 27, 35, 41, 47, 49, 72, 73] COPA,[38] LMA,[17, 18, 33, 41, 47, 49, 72, 73] and facial mask [25, 62] (Table III). Different methods ensure variable measurements of exhaled CO_2, and this value is important in order to observe the trend of $EtCO_2$ and evaluate the patient's hypo- or hyperventilation tendencies. A urinary catheter is useful for long procedures and for the diuretic effect of commonly administered mannitol. Despite these facts, some authors do not use urinary catheters,[8] particularly if the surgery lasts less than four hours.[5] Other authors use urinary catheters only for female patients.[45] A urinary catheter with a built-in temperature probe may be a good choice. Today, monitoring of the level of consciousness during anesthesia or sedation is possible using electroencephalographic analysis by Bispectral Index (BIS©, Aspect Medical Systems, Newton, MA, USA). This instrument may be useful during the sedation/anesthesia period and also to evaluate the level of responsiveness during awake cortical mapping.[18, 33, 47, 70] Most authors use clinical sedation scales such as the Ramsay Sedation Score [28, 39, 57, 71, 81] or the Mackenzie and Grant Score.[14, 25, 44, 83] Ghisi[84] suggests adopting the OAA/S scale[20] when performing MAC [8, 58] (Table I). Finally, Tijero *et al.* have proposed a possible intraoperative use for brain tissue oxygen pressure ($PtiO_2$) as a precocious local damage indicator in proximity of the surgical resection area.[39]

TABLE III.—*Airway devices related to anesthetic technique for awake craniotomy as reported in literature.*

Monitored anesthesia care	Asleep-awake-asleep
Nasal cannula	Cuffed oropharyngeal airway
Nasopharyngeal cannula	Laryngeal mask airway
Facial mask	Tracheal tube

Dexmedetomidine: the new alternative

Dexmedetomidine (Precedex©, Hospira Inc., Lake Forest, IL, USA) is a highly selective α_2-agonist with dose-dependent sedative, anxyolitic, and analgesic effects without ventilation suppression.[85] The primary action of α_2-agonists is the inhibition of norepinephrine release, causing excitation inhibition in the central nervous system. Compared to clonidine, dexmedetomidine has eight-times greater affinity for α_2-receptors and a shorter half-life.[86] Hall demonstrated that low-dose infusion of this drug in healthy volunteers provides sedation that can be easily reversed with verbal stimulation.[87] At clinical doses, patients remain somnolent without signs of paradoxical agitation or confusion. The analgesic effect of dexmedetomidine consistently reduces opioid administration even if it does not have the same efficacy.[88] In 1999, the American Food and Drug Administration approved dexmedetomidine use for sedation in intensive care units at a dose between 0.2 and 0.7 μg/kg/h. Except in the Czech Republic this drug is not available in Europe, where it is utilized as a sedative-analgesic only in veterinary medicine (Dexdomitor©, Orion Corporation, Espoo, Finland). In 2001, Bekker *et al.* reported the first application of dexmedetomidine combined with LMA (spontaneous breathing), fentanyl, sevoflurane (0.3-0.7%), nitrous oxide (70%), and BIS monitoring in an awake craniotomy.[71] In 2004, Fogarty Mack's group evaluated dexmedetomidine administration in five patients managed by MAC and five patients under an AAA approach. In this study, the AAA anesthetic approach was judged to result in more intraoperative discomfort.[57] Contrary to the study by Bustillo *et al.* pub-

lished in 2002, this report underlined that neurocognitive testing was successfully completed in all 10 patients.[89] The same idea was sustained by Souter in a five-case report published in 2005.[58] In that same year, a prospective study carried out by Ard *et al.*[66] on 17 patients who underwent awake craniotomy (AAA technique) confirmed dexmedetomidine validity in reducing the incidence of adverse events. They also found that dexmedetomidine administration reduced the necessary amounts of other drugs and improved surgical work, probably related to induced cerebral flux decrease.[90] Recently, this drug has been used to treat intractable discomfort in patients sedated with a propofol and remifentanil combination.[81] Ard[70] and Everett[91] demonstrated successful dexmedetomidine sedation in the pediatric population. Various dosages have been described from different authors. Generally, a dexmedetomidine load of 0.5 to 1 μg/kg/h over 20 minutes is followed by infusion at rates of 0.1 to 0.7 μg/kg/h to 20 minutes prior to testing. During cortical mapping the infusion rate is usually set to 0.1 to 0.2 μg/kg/h.

Awake craniotomy in children

Awake craniotomy reports in children are limited. In 1954, Pasquet wrote that children under 10 years of age would not tolerate awake craniotomy.[92] In the Archer series of 354 cases, the youngest patient was 12 years old.[12] In Welling's clinical report concerning neuroleptoanalgesia one of the four patients was 14 years old.[12] During the last ten years, numerous articles about awake craniotomy in children have been published. Some authors report successful procedures using a propofol and remifentanil-based MAC technique on patients 11-15 years old.[40, 61] Others describe dexmedetomidine sedation during a MAC protocol [91] or in combination with LMA and spontaneous breathing.[70] Finally, in 2004 Klimek reported his experience with a nine year-old boy using propofol sedation who was, accompanied by his father throughout the procedure.[93] In general all authors emphasize that such a procedure is feasible in very young people, and that children and parents must be adequately prepared and the children must be mature and psychologically ready.

Intraoperative complications

Awake craniotomy anesthetic care is complex and there is always a risk of intraoperative adverse events related to anesthetic technique and surgical manipulation. These problems may be classified as anesthesia-related and surgery-related complications (Table IV). The MAC approach that does not include airway control is vulnerable to airway obstruction. COPA usage for the AAA technique has caused airway obstruction in 15% of patients.[38] Hypoxia and oxygen desaturation events are more frequent during MAC and are commonly related to oversedation. In these cases, it is usually sufficient to speak to the patient, encouraging him to breath.

The incidence of intraoperative seizures during awake craniotomy is variable. With regards to tumor surgery, the intraoperative seizure incidence varies from 0% to 32% (Table II). Remifentanil appears to be associated with fewer intraoperative seizures than other opioids.[3, 33] Propofol administration has a protective effect against seizures but also must be discontinued 15 minutes before cortical stimulation so as not to interfere with EcoG. A higher incidence of seizures may be observed under neuroleptic analgesia.[14] According to Szelényi *et al.*, the train-of-five stimulation technique has a significantly lower incidence of stimulation-associated seizures than the 60 Hz technique.[32] Interestingly, according to the same author, patients with symptomatic epilepsy are not at a higher risk of intraoperative stimulation-associated seizures than patients without symptomatic epilepsy during awake tumor resection.[32]

Seizures may be focal and short, and are often related to cortical electrostimulation. Myoclonic twitches of one or two extremities typically terminate at the end of each electrical stimulus, and if they continue they may be controlled with brain ice Ringer's lactate irrigation [94] or administration of benzodiazepines (midazolam 2-5 mg *i.v.*). Generalized seizures like tonic-clonic seizures are less frequent and must be treated with brain cold Ringer's lactate irrigation, benzodiazepines infusion (midazolam 2-5 mg, diazepam 5-10 mg), or thiopentone sodium administration (25-50 mg). Most seizures, focal or general, self-terminate or are terminated by ice solution irrigation. The administration of propofol, benzodiazepines, or barbiturates is not usually the best choice because

TABLE IV.—*Classification of intraoperative complications that may occur during awake craniotomy.*

Anesthesia-related	Surgical-related
Airway obstruction	Focal seizures
Desaturation/hypoxia	Generalized seizures
Brain swelling	Aphasia
Hypertension/hypotension	Bleeding
Tachycardia/bradycardia	Brain swelling
Nausea/vomit	Venous air embolism
Shivering	Conversion to general anesthesia
Local anesthetic toxicity	
Pain	
Poor cooperation/agitation	
Conversion to general anesthesia	

it changes the cortical excitability and interferes with EcoG. During the postcritical period, ventilation must be accurately monitored.

Nausea is another frequent and important adverse event that is troublesome for the patient and that may make the patient agitated and uncooperative. Nausea and vomiting are prevented by administering antiemetics. Unfortunately, these conditions cannot be easily controlled if they are related to *dura mater* or brain vessel traction.[14, 42] Hemodynamic complications are usually well-controlled. Beta-blockers such as labetalol and esmolol are the most commonly used for arterial pressure increase.[39, 45] Urapidil, a really titratable drug, may be used successfully for hypertension during awake craniotomy.[6] Large blood losses are not common, and cardiovascular homeostasis depends on the site and dimension of the lesion. During the procedure shivering may occur, must be prevented by using warm infusions and blankets. Clonidine, dexmedetomidine, meperidine, tramadol, nefopam, and ondansetron are all useful medications for shivering prevention.[95] There are few cases of local anesthetic toxicity [11] (Table II). During surgery, pain may arise from poorly-anesthetised areas (often in the temporal area) and from *dura mater* and brain vessels. In these cases, additional local anesthetic infiltration is indicated. Since this type of procedure is very long, postural related pain may occur and is managed by allowing the patient small movements and by administering drugs such as acetaminophen,[42] diclofenac,[45] novaminsulfon,[42] and fentanyl.[8] Poor cooperation and agitation may be related to pain, anxiety, excessive sedation, seizures, and inadequate intraoperative psychological support. Venous air embolism is another rare adverse event. The occurrence of venous air embolism has a high variable incidence (10-80%) in neurosurgical cases performed in sitting position.[96] Use of the sitting and semi-sitting positions increases the risk of venous air embolism during awake craniotomy. Furthermore, spontaneous breathing raises the pressure gradient between the surgical site and the right atrium, favoring air suction. However, awake craniotomy is typically performed in the lateral or supine positions, so venous air embolism reports are not frequent.[97, 98] Balki reported a 0.64% incidence (3 out of 470 cases) and suggests the use of an intraoperative precordial Doppler monitor in the event of air embolism suspicion.[98] Table II summarizes intraoperative complications from the major published studies about awake craniotomy.

Patient perception and tolerance of awake craniotomy

There is little information about patient perception and tolerance of awake craniotomy. Many reports conclude that different anesthetic techniques allow this procedure to be feasible, safe, and well-tolerated [8, 14, 17, 33, 35, 47] even if these considerations are not always supported by objective data.[17, 33, 37, 47] However, some authors have focused their attention exactly on this matter. In 1997, Herrick *et al*. compared neuroleptoanalgesia with propofol-based PCS, and found that patients considered themselves to be satisfied with intraoperative comfort and pain.[14] This opinion slightly improved one month after surgery and patients, mostly in PCS group, said that they would be prepared to undergo the procedure again if necessary. In 1998, Danks designed a specific study to assess the subjective experience of patients undergoing awake craniotomy with the MAC approach (21 cases).[35] Three-quarters of those patients recalled none or only short portions of the procedure despite being awake for a substantial portion of the procedure (but all patients were premedicated with midazolam and 76% of patients were sedated with the same drug throughout the surgery). One-half of the patients stated that they did not recall suffering any intraoperative pain, anxiety, or discomfort. Only one patient recalled severe pain. Seventy-one percent of patients expressed

complete satisfaction with the procedure, and only two patients (9.5%) assigned a negative satisfaction score (score of 5 on a scale of 1 to 10 overall) to the experience. Eighty-one percent of patients stated that they would be prepared to undergo awake craniotomy again if indicated. Interestingly, two out of the three patients who said that they would not undergo the procedure again had rated an overall satisfaction score of 30 out of a possible 30. At the one-month interview, only one patient, with a worse prognosis than expected, showed a worsened mood. In 2005, a similar Scottish study reported analogous results.[49] This research confirms the tolerability of awake craniotomy, suggesting the necessity for a multicentric study and adequate multifactorial evaluation of the technique. Finally, in 2006 Manninen compared the efficacy of remifentanil to fentanyl in combination with propofol in providing MAC sedation for awake craniotomy.[8] This study assessed patients' satisfaction with both techniques at 1 h, 4 h and 24 h after surgery. Sixty percent of the patients recalled none or short portions of the procedure (without benzodiazepines premedication), 56% reported moderate pain, 22% reported no pain, and over 90% expressed complete satisfaction with anesthetic care. Considering the literature and personal experience, it could be asserted that awake craniotomy is well-tolerated. It is always necessary to look for patient's maximum psychophysical well-being before and throughout the operative procedure. The use and evaluation of a pain score, such as the Verbal Numerical Scale,[99] helps to avoid underestimating the patient's referred pain. It would be helpful for all institutions to evaluate their anesthetic care protocol by psychometric and satisfaction tests in order to optimize their work.

Future perspectives of awake craniotomy anesthetic care

In the future, many surgical and anesthetic changes will concern awake craniotomy techniques. Specific studies could demonstrate which anesthetic approach, MAC or AAA, is the safest and best-tolerated. New studies could also establish which airway device is most effective in making the procedure easier and safer. Until today, many solutions have been proposed on this issue without unanimous consent. Dexmedetomidine seems to be the best drug for awake craniotomy. Propofol, remifentanil, and, dexmedetomidine intravenous infusions will always be based on TCI algorithms to achieve safer and more predictable outcomes. More complex technological systems, such as closed-loop anesthesia, may find a good field of application in this context. Today, some infusion systems can be implemented with depth of sedation monitoring such as BIS. Furthermore, Gentilini has proposed an arterial pressure-based algorithm for alfentanil infusion.[100] With regards to awake craniotomy and neurosurgery, closed-loop control systems for mechanical ventilation can be extremely useful to control $EtCO_2$.[101] With regards to local anesthetic toxicity, levobupivacaine could replace bupivacaine for scalp block. Some authors have described this procedure performed without Mayfield's head holder,[28, 66, 102] this is possible using new electromagnetic navigation systems based on a sensor attached to the mastoid of the patient.[28] This technical solution avoids head fixation, allowing for minimal movement of the patient, reducing pain incidence, and facilitating anesthetist intervention on the patient's airway if necessary. Some authors have proposed to perform awake craniotomy as a day-hospital regimen. Taylor's study, based on 2 305 cases which underwent neurosurgery, reported a postoperative hematoma incidence of 2.2%.[103] This research revealed that clinical signs of postoperative hematoma occur within 6 hours following surgery due to active bleeding in the surgical site, and 24 hours after the procedure related to intracranial pressure and edema around the hematoma. Based on these findings, Blanshard *et al.* studied early discharge of 241 patients after awake craniotomy.[5] They concluded that selected patients, who had no intraoperative complications and received adequate instructions, may be discharged after a 6 hour postoperative observation period if they live near a hospital and have satisfactory assistance at home (15 patients of 241 in the study group -6%). In 2006, Manninen reported that 22% of 50 patients who underwent awake craniotomy under combined propofol and remifentanil or fentanyl MAC sedation were discharged the same day of surgery.[8] Obviously, these data are impressive but need to be confirmed in larger prospective studies.

The psychological aspect of awake craniotomy must be thoroughly examined. It would be extremely useful to develop a multidisciplinary approach to this matter with regards to procedure organization and patient management throughout the hospitalization. Neurosurgeons and anesthetists may adequately manage most patients, especially if the medical team is experienced. For scared and psychologically weak patients, the specialist's support could be decisive. Another interesting idea could be allowing postoperative patients to meet people who have yet to undergo awake craniotomy.

According to Bernstein *et al*. studies, awake craniotomy is a practical and effective standard surgical approach to supratentorial tumors, and could provide an excellent alternative to craniotomy under general anesthesia because it allows for cortical mapping and reduces intensive care time and total hospital stay.[104, 105] Bernstein's group has exceeded the uncertainty regarding surgical indications for awake craniotomy for tumor resection. On the contrary, in some centers awake craniotomy is not performed or is reserved only for tumor resection involving language areas. Many neurosurgeons perform tumor resection near motor and somatosensorial cortices guided by motor-evoked and somatosensory-evoked potential monitoring. Bernstein's approach could be considered excessive, however, in the meantime, it is not ethically acceptable to deny patients with tumors near functional cortices the option to undergo awake craniotomy. Surprisingly, Gupta *et al*. have recently published a study that indicates that surgery under general anesthesia is more efficacious than surgery under awake conditions for eloquent area lesions (no statistical significance between the two groups).[106]

Since the 1980s, patients affected by low-grade gliomas have been the most frequent group subjected to awake craniotomy in order to obtain the most complete resection, minimize postoperative morbidity and high-grade malignant degeneration, and delay tumor recurrence. Today, aggressive tumor resection does not appear to influence patient mortality.[107, 108] However, recently, surgical indications are often extended to involve resection of functional area metastases, meningiomas, and high-grade gliomas. Surgical indications for high-grade tumors are controversial: aggressive resection of these gliomas can increase survival time but it is always necessary to evaluate the expected survival of the patient related to the risk of postoperative deficits.[109, 110] In the future, cortical mapping in combination with emerging functional brain mapping techniques (fMRI, positron emission tomography, magnetoencephalography, intrinsic optical signals, transcranial magnetic stimulation) will optimize surgical techniques and indications.

Conclusions

Awake craniotomy for tumor resection involving functional areas is a surgical approach that offers great advantages with respect to patient outcomes. This is a complex technique that requires great patient and equipment engagement. In this type of procedure, the anesthetist's goal is to provide a safe and effective operation and to reduce the patient's psychophysical distress. The choice of the anesthetic technique, MAC or AAA, must be related to the anesthetist's capability and experience. AAA, even if more complex, allows the advantages of avoiding breathing depression and access to airway protection, consequently decreasing intraoperative complications. The AAA technique may be preferred for delicate and more complex patients. Today, all of these ideas have not yet been demonstrated by any one study. The large number of different airway control techniques performed during awake craniotomies in the literature confirms that an optimal *modus operandi* does not exist. Dexmedetomidine, not yet available in Europe, appears to be the best drug for sedation without interference with respiratory function. For the moment, propofol and remifentanil are the most-used drugs for this procedure. Particularly, TCI infusion systems allow better drug titration, avoiding oversedation and respiratory depression. Depth of anesthesia monitoring systems, like BIS, are useful in this kind of surgery even if clinical observation of vital signs and specific sedation scores are adequate to manage this type of patients. International studies indicate that awake craniotomy is well-tolerated and only moderately burdened by intraoperative complications. Personal experience, careful planning, and attention are the basis for obtaining good results. Additional studies are needed to optimize awake craniotomies in order to increase tolerability and decrease the incidence of complications.

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Address reprint requests to: F. Piccioni, Department of Anesthesiology and Intensive Care, IRCCS Foundation, National Cancer Institute, Via Venezian 1, 20133, Milan, Italy. E-mail: fedepic@libero.it