Failed awake craniotomy: a retrospective analysis in 424 patients undergoing craniotomy for brain tumor

Clinical article

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Object. Awake craniotomy for removal of intraaxial tumors within or adjacent to eloquent brain regions is a well-established procedure. However, awake craniotomy failures have not been well characterized. In the present study, the authors aimed to analyze and assess the incidence and causes for failed awake craniotomy.

Methods. The database of awake craniotomies performed at Tel Aviv Medical Center between 2003 and 2010 was reviewed. Awake craniotomy was considered a failure if conversion to general anesthesia was required, or if adequate mapping or monitoring could not have been achieved.

Results. Of 488 patients undergoing awake craniotomy, 424 were identified as having complete medical, operative, and anesthesiology records. The awake craniotomies performed in 27 (6.4%) of these 424 patients were considered failures. The main causes of failure were lack of intraoperative communication with the patient (n = 18 [4.2%]) and/or intraoperative seizures (n = 9 [2.1%]). Preoperative mixed dysphasia (p < 0.001) and treatment with phenytoin (p = 0.0019) were related to failure due to lack of communication. History of seizures (p = 0.03) and treatment with multiple antiepileptic drugs (p = 0.0012) were found to be related to failure due to intraoperative seizures. Compared with the successful awake craniotomy group, a significantly lower rate of gross-total resection was achieved (83% vs 54%, p = 0.001), there was a higher incidence of short-term speech deterioration postoperatively (6.1% vs 23.5%, p = 0.0017) as well as at 3 months postoperatively (2.3% vs 15.4%, p = 0.0002), and the hospitalization period was longer (4.9 ± 6.2 days vs 8.0 ± 10.1 days, p < 0.001). Significantly more major complications occurred in the failure group (4 [14.8%] of 27) than in the successful group (16 [4%] of 397) (p = 0.037).

Conclusions. Failures of awake craniotomy were associated with a lower incidence of gross-total resection and increased postoperative morbidity. The majority of awake craniotomy failures were preventable by adequate patient selection and avoiding side effects of drugs administered during surgery.

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Key Words • awake craniotomy • brain • failure • seizure • tumor

Awake craniotomy is an established procedure for the resection of intraaxial lesions adjacent to or within eloquent brain regions.6,8,15,38,48 To ensure a successful awake craniotomy, several prerequisites should be met. Judicious patient selection is essential for precise mapping and reliable continuous monitoring. Preoperative preparation is pivotal in achieving patient cooperation, and a specialized team is needed to manage the scenario for optimal complications avoidance.5,33,34,38,39,44 Complications associated with awake craniotomy have been previously reported.1,16,22,23,25,34,36,38,43 However, the actual incidence of awake craniotomy failures, as well as possible causes, has not been well characterized. In the current study we reviewed our prospectively collected database of 424 awake craniotomy cases to identify and analyze the incidence and causes of failed awake craniotomy.

Methods

This retrospective study is based on prospectively collected data of patients undergoing awake craniotomy in the Tel Aviv Medical Center between 2003 and 2010. The study was approved by the Tel Aviv Medical Center Institutional Review Board.
Study Participants

Patients undergoing awake craniotomy for tumor resection of a supratentorial lesion located within or close to an eloquent area as determined by a preoperative MRI scan were included. Decisions regarding patient selection were made by the senior author (Z.R.) based on a subjective evaluation of each patient’s suitability for the procedure. Inclusion criteria were liberal to provide some chance of monitored resection even in patients with deficits. As a general guideline, cooperative, consenting patients, with some potential for monitoring (even with a preoperative language deficit) were selected to undergo an awake procedure. The rationale for this selection criterion was that even preservation of some language function may be better than none. Uncooperative patients, those with severe dysphasia prohibiting any cooperation, and those in whom severe preexisting anxiety was present were excluded.

An awake craniotomy was considered a failure if conversion to general anesthesia was required or if cortical mapping or awake monitoring were either aborted prematurely or not performed successfully.

Preoperative Evaluation

Preoperative evaluation of patients included a formal speech evaluation and a neuropsychological evaluation. The formal speech evaluation was carried out by the neurosurgeon until 2009. Beginning in 2010, speech evaluation was performed by a neurocognitive team. Language functioning was evaluated 1 or 2 days prior to surgery (baseline) and consisted of naming, visual and auditory verb generation, and comprehension. These tests were repeated intraoperatively as discussed below. The neuropsychological evaluation included a short interview with the patient and a family member followed by a battery of cognitive tests: Wechsler Adult Intelligence Scale–III Similarities and Digit Span, the Rey Auditory Verbal Learning Test, the Rey-Osterrieth Complex Figure Test, naming, verbal fluency (semantic and phonetic), Wechsler Memory Scale–III Spatial Span, and the Stroop test or the Montreal Cognitive Assessment test. Several questionnaires were administered to evaluate the patient’s emotional status and his or her ability to cope with surgery in an awake state. They included the Beck Depression Inventory, the State-Trait Anxiety Inventory (for quantifying anxiety), the Barratt’s Impulsivity Scale–II, and the Sensitivity to Reward and Punishment Questionnaire.

Preoperative Preparation

All patients met with our awake craniotomy team who described the procedure step by step, starting from hospital admission and continuing through preoperative preparation, the procedure itself, and the postoperative period. Our social worker was also available to escort the patients on the day of surgery and during the operation itself. Minimal doses of sedatives and anxiolytic drugs were generally administered on the morning of the operation. During the last 3 years of this study, we aimed for optimizing the anticonvulsant blood level by the evening prior to the operation.

Intraoperative Management

Anesthetic Management. Most patients received small doses of intravenous midazolam (1–2 mg) and fentanyl (50–100 μg) upon arrival to the operating room. In all patients scalp nerve blocks were performed according to the location of the planned pinning and incision site, that is, the supraorbital, temporal, or occipital nerve block with local anesthetics. Anesthesia monitoring included standard monitoring in addition to invasive blood pressure monitoring. Spontaneous ventilation was monitored by capnography. Urinary catheters were usually not inserted to reduce patient discomfort, and mannitol was not used unless absolutely required. All patients received oxygen (3 L/min) through a nasal cannula during the operation. Light sedation was maintained by short-term continuous administration of remifentanil in most patients. In selected patient populations, such as when sedation with remifentanil was not sufficient, propofol was carefully supplemented. As a general guideline, patients who exhibited a low baseline speech performance preoperatively did not receive propofol or remifentanil. All sedatives or analgesics were discontinued briefly after pinning to carry out a second neurocognitive evaluation after the patient’s head was immobilized and before beginning the skin incision. Patients who suffered any pain from dural manipulation received infiltration of 1% lidocaine between the dural leaves. Evaluation of performance in all tasks was assessed by comparing the accuracy and speed of response to the preoperative levels. Mild sedation and pain control medication were given after the resection was completed until wound closure.

Mapping. Stimulation was performed using a 50-Hz bipolar stimulator (OCS-2, Radionics, Inc.) with the following parameters: biphasic pulses, 500-μsec pulse width, and 2–3-second train duration. A standard bipolar probe was used with 0.5-cm spacing between electrode tips. Electrocorticography was performed using a Silastic embedded 8-contact strip electrode (Ad-Tech) placed in proximity to the exposure site and approximately 1–2 cm from the stimulation site for the closest contact and 7–8 cm for the farthest. In procedures in which dural-cortical adhesions precluded the electrode strip placement, subdural needle EEG electrodes (SpecMedica) were placed in at least 4 of the following scalp locations according to the International 10-20 System: C3, C4, F3, F4, P3, and P4, which were used to record EEG activity depending on the tumor site. These recordings were referenced to the Fpz location. All data were recorded and saved digitally using an intraoperative neurological workstation (NIM Eclipse, Medtronic). Either EEG or electrocorticography were analyzed online for detection of afterdischarges or epileptiform activity stemming from the cortical stimulation.

Stimulation for mapping was initiated at an intensity of 2 mA and increased stepwise by 2 mA to a maximum of 10 mA before claiming a specific cortical region negative for language or motor function. In positive language mapping, the area was restimulated 3 times to reproduce the functional deficit and to ensure that the cortical area is essential for language. Ten milliamperes was the upper limit to avoid seizures, which, from our experience,
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is sufficient a limit for positive eloquent cortex (motor as well as language) mapping. In addition, the stimulator used for mapping has an upper limit of generating 10 mA (OCS-2, Radionics, Inc.).

Afterdischarge potentials were captured, the amplitude used for stimulation was reduced by 2 mA, and the location that elicited the afterdischarge potentials was avoided if no functional deficits were caused at that site. In cases in which mapping was achieved, we did not re-stimulate that location, and an adjacent cortical area was remapped for confirmation.

**Monitoring.** Language monitoring was conducted using all aspects of speech production and comprehension in all patients. These included naming tasks, visual and auditory verb generation, definitions, and comprehension (as part of the definition tasks). The methods are described below.

Naming. This task was designed for mapping of pure pronunciation, visual object recognition, and naming. Patients were presented with pictures of concrete objects (for example, a car or a banana) from several semantic categories (for example, animals or clothing items) and requested to name them. Patients were asked to start each answer with the words “This is a ____ (name: “car”),” to separate pronunciation and naming processes.

Verb Generation. In this task, patients were requested to retrieve an appropriate verb describing an action related to a presented noun. Nouns were either presented visually (visual verb generation, using pictures of objects) or vocally (auditory verb generation, nouns were read to the patients). As different objects vary in the number of appropriate verb complements (for example, you generally eat a banana but you can live in, visit, or tour a palace), the test included objects of several difficulty levels and thus enabled sensitivity to the patient’s deficit in the task. The use of visual versus auditory verb generation was determined either by the patient’s baseline performance (when the patient’s performance was significantly better in one of the modalities) or according to the patient’s preoperative functional MRI findings. When there was no preference to one modality over the other, or when visual verb generation was preferred, visually presented pictures were used for the combined naming and verb generation task. In these cases, patients were asked to respond to each picture according to a fixed pattern: “This is a ____ (name: “ball”) and you ____ (verb: “play”) with it,” to isolate the performance in each task. This merge allowed for shortened duration of cortical mapping.

Definitions. In this task, patients were asked to retrieve nouns in response to verbally presented definitions (that is, the definitions were read to the patients). The test included definitions of concrete objects (for example, “a yellow sour fruit”—a lemon), as well as of more abstract nouns (for example, “teaches children in class”—a teacher), and was used to map semantic retrieval and sentence comprehension.

In patients with poor preoperative language function, simple language tasks (such as counting [1–20] or pronouncing the alphabet) were used for mapping of speech production, and simple instructions (for example, “Raise 2 of your right hand fingers”) for mapping of comprehension.

Following cortical stimulation and throughout the resection, language was monitored using free speech and conversation with the observer, which in its nature simultaneously combines several aspects of language functioning. When baseline function was poor, we used the most appropriate task according to the aforementioned criteria.

Motor function was evaluated according to the tumor location by asking the patient to perform various movements (for example, clenching fist or flexing foot) as well as the ability of the patient to plan and initiate movements in cases of lesions in proximity to the supplementary motor area.

**Intraoperative Management of Awake Craniotomy Failures.** The decision to abort the awake craniotomy was made by the senior surgeon. Propofol was used when general anesthesia had to be induced. In these cases, airway control was achieved by insertion of a laryngeal mask or by intubating the patient, and the surgery then continued as a tumor resection procedure under general anesthesia.

**Intraoperative Seizure Management.** Iced Ringer’s lactate was irrigated over the brain if seizures occurred clinically or when detected by electrocorticography during cortical stimulation. Sedatives were avoided to allow for uninterrupted functional mapping and clinical evaluation. After a seizure occurred, mapping was stopped for 5 minutes until the patient regained speech/motor abilities. Patients whose seizures were not controlled for longer than 5 minutes or had evolved into status epilepticus were given an additional loading dose of antiepileptic agent followed by induction of general anesthesia and urgent intubation as deemed necessary. The resection was then continued, taking all other standard safety precautions used in intraaxial tumor resection under general anesthesia.

**Statistical Analysis**

Descriptive statistics are given as the median, the mean ± SD for continuous variables, and frequency distribution for categorical variables. The chi-square or Fisher exact test was used to examine the differences between groups regarding categorical variables. The 2-sample t-test or Mann-Whitney test was used to compare groups for continuous variables. For repeated measurements a mixed-model repeated-measures ANOVA was performed. All statistics analyses were performed using SAS 9.2 for Windows.

**Results**

**Patient Population**

A total of 488 patients underwent awake craniotomy between 2003 and 2010. In 424 patients, complete medical, surgical, and anesthesiology records were available (238 men [56%] and 186 women [44%]). The mean patient age was 51.5 ± 16.1 years. The KPS scores were as follows: 332 patients (78%) scored within 80–100, 86 (20%) within 50–70, and 6 (1%) within 30–40. The lesion location and pathological diagnoses are listed in Table 1. The preoperative MRI studies revealed that most patients (308 [73%]) had a left-sided lesion. Gross-total resection
Patients Experiencing Failed Awake Craniotomy

Failed awake craniotomy was encountered in 27 patients (6.4%). In 9 patients (2.1%) reversion to general anesthesia was required due to seizures (n = 5), severe restlessness (n = 3), or acute brain edema (n = 1). All patients remained with the head fixed within the Mayfield head holder, and sterility was never compromised. In 4 of these 9 patients a laryngeal mask airway was inserted, 1 patient underwent fiberoptic intubation, and the other 4 patients underwent deep sedation without endotracheal intubation. Awake craniotomy failure in the other 18 patients was due to problems in intraoperative cortical mapping/monitoring such as severe dysphasia, restlessness, or somnolence.

Intraoperative Communication Difficulties

Communication difficulties in 18 patients did not allow for appropriate mapping or monitoring. Eleven patients could not communicate due to dysphasia; 6 had severe pre-existing dysphasia and 5 had moderate preoperative dysphasia but speech deteriorated during surgery to the extent that precluded effective language monitoring. Eight of the 18 patients had received loading or partial loading doses of phenytoin upon arrival to the operating room, which may have accounted for the reduced communication.

Seven patients could not communicate due to somnolence (n = 2) or restlessness (n = 5) that developed during surgery. All of these patients received intravenous phenytoin on arrival to the operating room and intravenous propofol during the first stage of the surgery.

Compared with the successful awake craniotomy group, more patients in the communication-related failed awake craniotomy group had KPS scores lower than 70 (39% vs 21%, p = 0.07). Phenytoin was the only AED significantly associated with communication and awake craniotomy failures (78% of the failed awake craniotomy group vs 41% of the successful awake craniotomy group, p = 0.0019). There were more patients in the awake craniotomy failure group presenting with preoperative mixed dysphasia, when compared with the successful awake craniotomy group (44% vs 7%, p < 0.001). We did not find any statistically significant differences between the successful group and the failed group with respect to demographic variables, tumor variables, comorbidities, anesthetic variables, intraoperatively administered drugs, or perioperative sodium levels.

Intraoperative Seizures

Intraoperative seizures occurred in 49 patients (11.6%). In 9 patients, seizures led to either a new language deficit that did not enable reliable monitoring of language, or to a postictal state that did not enable mapping or monitoring of any function.

Three patients experienced a seizure before cortical mapping while the other 6 patients had seizures induced by cortical stimulation. In 5 patients, seizures were intractable and evolved into generalized seizures with loss of consciousness.

Sixteen percent of patients with a preoperative history of seizures experienced intraoperative seizures compared with 8% of patients who did not have a seizure history (p = 0.024). Moreover, 7 patients (4.3%) in the seizure-related failure group had a history of seizures compared with 2 patients (0.8%) in the failure group without a seizure history (p = 0.03). A greater proportion of patients in the failure group used multiple AEDs than in the successful group (66.7% vs 16.4%, p = 0.0012). The type of AED, timing of loading, or blood levels of AED did not affect the incidence of intraoperative seizures.

Resection Outcome

A significantly lower rate of GTR was achieved in
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the failed awake craniotomy group than in the successful group (54% vs 84%, p = 0.008).

Gross-total tumor resection in patients with preoperative dysphasia was achieved in 79.4% of our patients compared with 75% of patients in whom successful monitoring had failed. Gross-total resection was achieved in 62.5% of patients in the failure group who had preoperative severe mixed dysphasia.

**Neurological Outcome**

Compared with the successful awake craniotomy group, there was a significantly higher incidence of short-term speech deterioration among the failure group (6.1% vs 23.5%, p = 0.0017). At 3 months postoperatively there was improvement in both groups, but with significant differences between groups in favor of the patients with successful awake craniotomy (2.3% vs 15.4%, p = 0.0002). There was no difference between the successful and failure groups with respect to motor function outcome.

**Complications**

One patient in the failure group died postoperatively. In this patient, a new atrial fibrillation developed on postoperative Day 2, followed by hemodynamic instability and cardiac arrest. Major complications (such as hematoma requiring emergency repeat craniotomy) occurred in 4 (14.8%) of 27 patients in the failed awake craniotomy group vs 16 (4%) of 397 patients in the successful awake craniotomy group (p = 0.037).

The length of hospital stay was significantly longer for the failure group than the successful group (8.0 ± 10.1 days vs 4.9 ± 6.2 days, p < 0.001).

**Discussion**

Previous studies have described the general and neurological outcomes of awake craniotomy. Others reported major intraoperative complications during awake craniotomy, such as air embolism, brain swelling, trigemino-cardiac reflex, or seizures requiring intubation and induction of general anesthesia. These studies have not, however, provided the actual incidence of aborted cases, or failure, of awake craniotomy, nor have they specified the causes of the failures. The major findings of the present study in 424 patients undergoing awake craniotomy are as follows: 1) In an experienced neurosurgical center, awake craniotomy is a feasible procedure with a failure rate of 6.4%. 2) Failed awake craniotomy resulted in lower rates of GTR, increased neurological morbidity and complication rates, and a longer length of hospital stay when compared with successful awake craniotomy. 3) Failed awake craniotomy was more prevalent in patients with a history of seizures, those treated with multiple AEDs, those treated specifically with phenytoin, and those who presented with mixed dysphasia.

**Awake Craniotomy Failures and Outcome**

Our study demonstrates that failure of awake surgery negatively affects outcome. There was a significantly lower rate of GTR among the failure group than among the successful group. Interestingly, our data show that the majority of patients with severe language deficits can still enjoy a successful monitored resection although at a somewhat lower success rate than patients with less severe or no preoperative language deficits. Moreover, operative complication of a failed awake craniotomy might be related to the specific cause of failure; for example, severe restlessness of the patient may result in Valsalva maneuvers or uncontrollable hypertension, which might cause imperfect hemostasis or brain swelling with neurological deterioration.

Indeed, we found that the immediate postoperative neurological outcome was worse among the failure group. There was also a higher rate of major complications in the failure group compared with the successful group as well as a longer hospitalization period. Although several qualitative studies have shown good results in term of patients’ experiences with awake surgery, a failure in this procedure might result in severe impact on patient’s satisfaction and quality of life.

**Causes of Awake Craniotomy Failures**

In the current series of 27 failed cases of awake craniotomy, two-thirds of the failures were due to severe dysphasia or severe somnolence or restlessness. Additionally, the data showed that mixed dysphasia and perioperative phenytoin treatment were associated with more failures. There was a tendency toward communication-related awake craniotomy failure in patients presenting with KPS scores lower than 70 (p = 0.07). These failures might have been avoided by following a more stringent patient selection protocol as already advocated by others. Previous studies reported that AEDs, especially phenytoin, might cause severe cooperation difficulties, somnolence, delirium, acute visual dysfunction, acute meningoencephalitis, confusion, lethargy, and coma. Thus, we may conclude that trying to avoid phenytoin loading during surgery may be of benefit. If required, it may be advised that loading the patient with phenytoin will take place 1 or 2 days prior to surgery, while monitoring blood levels and adjusting drug doses accordingly.

Sedative drugs, such as propofol, fentanyl, or remifentanil, may also cause somnolence. Some centers use the asleep-asleep-asleep technique for awake craniotomy for which the anesthetic method includes moderate sedation with the administration of the aforementioned sedatives until the beginning of the mapping part of the operation. Our experience indicates that it was easy to control intraoperative anxiety and pain with local anesthetics, regional blocks, and minimal doses of anxiolytic and pain medications, thus avoiding the need for conversion of awake craniotomy to general anesthesia as a result of oversedation.

Seizures may result in difficulties in awake craniotomy, ranging from mild inconvenience to the patient and surgeon to uncontrolled generalized seizures and/or postictal state necessitating conversion to general anesthesia. Seizures may evolve particularly during cortical stimulation for mapping. Threshold levels should be as low as possible to elicit a response without producing seizures. Szelényi et al. reported that there were well-established threshold levels for each functional area in cortical stimu-
lation for mapping purposes. They also advocated that areas that elicited a seizure should not be restimulated to avoid generalizing of the epileptic activity. There are several reports in the literature regarding seizures during awake craniotomy. Sartorius and Wright reported a 5%–20% rate of intraoperative seizures. In a large cohort of patients undergoing awake craniotomy (n = 511), Serletis and Bernstein reported a seizure rate of 4.9%. In our series the number of intraoperative seizures was found to be within the range of those reported in the literature. According to our data, patients in whom seizures were the presenting symptom were more likely to seize intraoperatively. Moreover, these patients had a higher risk of failure due to seizure, especially those who were treated with multiple AEDs. To the best of our knowledge, only 1 study reported the actual rate of awake craniotomy failures due to generalized seizures: in their series of 511 patients who underwent awake craniotomies, Serletis and Bernstein reported on 2 patients who required conversion to general anesthesia due to generalized seizure. In our study, 5 of 424 patients undergoing awake craniotomy required conversion to general anesthesia due to generalized seizures.

**Study Limitations**

The limitations of this study are those inherent to a retrospective study of small diverse clinical populations. Additionally, during the 8 years of this study we have generated a learning curve of the awake craniotomy team that has changed and improved the awake craniotomy protocols. Specifically, on examination of our patient selection process, preoperative cognitive, language, and behavioral evaluations were not constructed by a professional neurocognitive team during the first several years of this project. Also, our management strategy of optimizing the AED levels prior to surgery, as well as supplementing lower doses of sedative drugs, was applied only during the last 4 years.

**Conclusions**

The nature of the causes of failure in our cohort serves to emphasize the essential need for professional multidisciplinary teamwork to enhance the likelihood of successful awake craniotomy. The process begins with a stringent patient selection process and continues throughout the many facets of the patient’s management by the neurosurgeon, the neuropsychologist, the anesthesiologist, and the social worker. The results of the present study suggest that most monitoring and mapping failures of awake craniotomy are preventable by meticulous patient selection and avoidance of drugs that might change a patient’s cognitive status. While there will undoubtedly be failures in awake craniotomy, the purpose of the report is to identify variables that may minimize the incidence of failure. However, even with the best screening methods, there will always be patients who appear suitable before the operation, but will show some language/cognitive decline during surgery to the extent that no valuable monitoring is feasible.

Successful awake craniotomy was associated in our patients with a better surgical and functional outcome.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ram, Nossek, Matot. Acquisition of data: Nossek, Barzilai, Rapoport, Gonen, Sela, Korn. Analysis and interpretation of data: Ram, Nossek, Matot, Rapoport, Gonen, Sela, Hayat. Drafting the article: Ram, Nossek, Shahar, Barzilai, Rapoport, Sela, Hayat. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ram. Statistical analysis: Nossek. Administrative/technical/material support: Nossek, Korn. Study supervision: Ram, Matot.

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