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Review

Is a wake-up call in order? Review of the evidence for awake craniotomy

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ABSTRACT

Awake craniotomy (AC) has been used in increasing frequency in the past few decades. It has mainly been used for resection of intrinsic tumors, but also, rarely, for other pathologies. The vast majority of reports specific to one pathology, however, have focused on resection of low grade glioma in the awake setting. Tumors in eloquent areas have mainly been resected when the patient is awake for the purpose of preservation of function. Motor function is the most documented, and most successfully preserved function. Other functions are harder to localize with direct electrical stimulation (DES), and thus more difficult to preserve. The success rate of DES localization correlates to the rate of function preservation. The effect of AC on extent of resection is inconsistent in the literature. Other functions, such as sensory and visuospatial recognition, have been protected during AC, but this is best performed in large, referral centers that have experience with the procedure. Other benefits to AC, such as cost-effectiveness and reduction in patient pain and anxiety, have also been reported.

1. Introduction

Awake craniotomy (AC) has been used for resection of a wide variety of pathologies [1–4]. Its use has expanded significantly over the last decades [2,5–7], and both the indications and techniques are continuously evolving. AC has been utilized for resection of vascular lesions, epileptic foci, and rarely, extrinsic brain tumors [3,8–11], but the main role for AC has been for resection of intrinsic brain tumors, mainly low grade glioma (LGG), high grade glioma (HGG) and cerebral metastases.

Many reasons to undertake craniotomies in the awake setting have been quoted in the literature, of which the most important is the potential to decrease the likelihood of injury to eloquent areas of the brain. An AC enables the surgeon to monitor the function of a center, or tract, during an awake resection which, in turn, is thought to decrease the likelihood of a new neurological deficit or worsening of an existing deficit following the resective operation. The second reason to perform a craniotomy in the awake setting is the potential for an increased extent of resection (EOR), because of the increased confidence in the safety of the resection provided by the awake monitoring. Other advantages of an AC when compared to a craniotomy under general anesthesia (GA) are the reduced cost of functional monitoring compared to continuous neurophysiological monitoring.

In this article we review the available literature, and discuss evidence for any of the advantages described. The review will focus on the clinical controversies surrounding AC, including evidence of benefit for the different tumor pathologies resected in the awake setting, the effect an awake resection might have on the EOR, and the evidence for preservation of various functions in AC. Finally, we will consider other advantages for resection with an AC.

2. Which tumors should be resected using an AC?

The majority of the data available in the literature is related to resection of primary brain tumors. To our knowledge, there has been no report of a series – neither retrospective nor prospective – of AC used for the exclusive resection of metastases.

Furthermore, although there have been case series reports [12–15], there has also been no series limited to HGG resection in AC, to our knowledge. Many authors have reported on unselected cohorts of primary brain tumors or intrinsic tumors, but none were selective for HGG. This may stem from the fact that HGG are often more easily separated and distinguished from the surrounding brain. This is particularly true with the advent of intraoperative fluorescence-assisted resection, which has been shown to improve EOR [16,17]. Furthermore, HGG commonly displace or destroy cortex and white matter tracts, whereas LGG may infiltrate them [18].

Many authors have described the use of AC for groups of patients harboring different grades of glioma [6,19–23]. The result of mixed

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series cannot be easily generalized, because the expected survival and clinical courses are very different for different pathology grades of primary brain tumors. Furthermore, the assessment for EOR cannot be unified between tumors that enhance with gadolinium and those that have no enhancement. Thus, many of these reports serve to demonstrate the specific approaches in different centers, and the technical utility of awake resection in gliomas of various grades rather than the actual effect on patient outcome. In some of these reports, awake resection has been combined with intraoperative imaging to facilitate extended resection [1,24–26]. As mentioned, these did not serve to test the outcomes, but to describe the use of the combined modalities in glioma surgery.

In comparison to those reports described earlier, which were not selective to tumors based on pathology, several articles focused only on awake resection of LGG [7,26–28].

Duffau et al. compared two cohorts, one before (1985–1996) and one after (1996–2003) the implementation of direct electrical stimulation (DES) in resection of LGG. [29] In the later cohort, AC was used for all LGG, whether or not the tumor was in an eloquent area. The authors were able to achieve a total resection in 25.4%, compared to 6% in the GA group. This difference in EOR was statistically significant. Furthermore, the rate of neurological deficit was lower in the AC group (6.5% *versus* 17%, $p < 0.019$). The results presented should be interpreted cautiously: the before-*versus*-after design, and the lack of a control group make the results difficult to generalize. For instance, the earlier group operated under GA, had 35% of tumors located in eloquent areas, whereas the second group had 62.3% of tumors in eloquent areas. Whether this difference relates to widening of the center's referral base or to other factors, it is clear that the two groups were different from each other. Conclusions drawn from this study may be severely biased. Nevertheless, the data suggest that perhaps AC is especially suited for resection of LGG, and improves outcomes in resection of these tumors.

Martin et al. described their experience with a prospectively collected series of 25 patients undergoing intraoperative MRI-controlled AC for resection of LGG [26]. They did not describe outcome in statistical terms, and the group was not controlled. However, they did report that only one patient (4%) suffered a persistent postoperative deficit. The authors were the first to describe their protocol and the details of the procedure for the combination of AC and intraoperative MRI.

De Benedictis et al. reported on nine patients who were reoperated in a referral center in Montpellier following prior resection of LGG in other institutions. The unique feature in this report was that a direct comparison was made in the same patient between resection in the GA setting (the previous operation) and resection in the awake scenario (in the referral center). In these nine patients, the authors described advantage for the awake resection in two elements. Firstly, the severity of neurological deficit after the operation was reported to be relatively low. Of the nine patients, three had a normal neurological examination immediately postoperatively. Four patients had transient worsening of speech difficulties, and two others had mild inaccuracy in movements or dysesthesia. Furthermore, the EOR was greater in the AC group; from three subtotal resections and six partial resections under GA, the authors were able to achieve total resection in five patients and a subtotal resection in the remaining four using AC. It is noteworthy, however, that as all the patients were referred to the referral center for the purpose of AC, the group was significantly biased toward suboptimal resection under GA.

Wilden et al. reported on a small group of seven patients who were operated using AC for resection of LGG [7]. Their results were excellent, with only one patient suffering a persistent neurological deficit. The majority of patients (6/7) underwent subtotal resection in this report.

In one of the largest series in the literature, Chang et al. retrospectively reviewed 281 patients who were operated in the University of California in San Francisco, USA, for resection of LGG [30]. One hundred and twenty-seven of these underwent intraoperative mapping to determine if the suspected eloquent area was in fact a "true-eloquent" area or a "false-eloquent" area. Of the 127 patients who underwent mapping, 81 were found to have positive mapping, meaning that tumor was found to infiltrate a functional area, and the remaining 46 had negative mapping, meaning that the suspected eloquent location was not confirmed with intraoperative mapping. Those patients with true-eloquent tumors had a significantly shorter overall survival compared to those with false-eloquent tumors. In fact, those patients who had true-eloquent tumor had an overall survival similar to those who did not undergo mapping at all. Not all patients in this group underwent mapping and stimulation in an awake setting. Some of the mapping of motor areas was done with the patient under GA, and this was at the operating neurosurgeon's discretion. Still, this large report stresses the significant effect of mapping eloquent areas during resection of LGG on overall survival.

In summary, AC and eloquent area mapping have mainly been used and reported for the resection of LGG. The results are described in the following sections.

Rarely, AC has been used for resection of extraaxial tumors or for vascular lesions [10,31–33]. The data are too limited to conclude that the procedure is recommended for either of these pathologies and should be tailored to the specific circumstances.

3. Does AC affect EOR?

The main purpose of AC is preservation of function in eloquent brain areas during tumor resection. The effect AC has on the EOR is unclear. It may be hypothesized that the awake setting would limit the ability to continue the resection after the point of neurological deficit, even if that deficit would eventually recover, and the EOR would thus be lower. However, the opposite may also be stipulated: perhaps areas of tumor that would not be explored in the asleep setting, due to potential eloquence, may be resected safely in the awake setting. It is noteworthy that critical evaluation of both EOR and neurological outcome may prove difficult. Prospective studies are unselective for tumor pathology, since the pathology is unknown at the time of designation to AC or craniotomy under GA. Retrospective studies, in contrast, are always subject to selection bias, where the decision to operate with the patient awake may have been influenced by the neurosurgeon's anticipation of resectability and the potential for neurological deficits.

Meyer et al. performed AC on 65 patients with primary intraaxial tumors [19]. Fifty-one were found to have HGG, and 14 were diagnosed with LGG. The goal of all operations was to achieve the maximal resection until a neurological deficit was demonstrated. The cohort was not controlled, but in only 52% of the patients was a resection of over 90% reached. It is hard to conclude whether a different EOR would be attainable with craniotomy under GA, but intraoperative neurological deficit was evident in 74% of the patients, thereby terminating the resection. It may be inferred from this data that the clear demonstration of a neurological deficit might, in large numbers, lead to a limitation of resection, thereby causing a decrease in the EOR.

Pereira et al. prospectively collected their data of 79 patients who underwent AC for resection of primary brain tumors [34]. The authors reported gross total resection in only 31.6% of the