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ORIGINAL ARTICLE - BRAIN TUMORS

Awake craniotomy versus craniotomy under general anesthesia without surgery adjuncts for supratentorial glioblastoma in eloquent areas: a retrospective matched case-control study

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Abstract

Background Awake craniotomy with electrocortical and subcortical mapping (AC) has become the mainstay of surgical treatment of supratentorial low-grade gliomas in eloquent areas, but not as much for glioblastomas.

Objective This retrospective controlled-matched study aims to determine whether AC increases gross total resections (GTR) and decreases neurological morbidity in glioblastoma patients as compared to resection under general anesthesia (GA, conventional).

Methods Thirty-seven patients with glioblastoma undergoing AC were 1:3 controlled-matched with 111 patients undergoing GA for glioblastoma resection. The two groups were matched for age, gender, preoperative Karnofsky Performance Score (KPS), preoperative tumor volume, tumor location, and type of adjuvant treatment. Primary outcomes were extent of resection and the rate of postoperative complications. The secondary outcome was overall postoperative survival.

Results After matching, there were no significant differences in clinical variables between groups. Extent of resection was significantly higher in the AC group: mean extent of resection in the AC group was 94.89% (SD = 10.57) as compared to 70.30% (SD = 28.37) in the GA group ($p = 0.0001$). Furthermore, the mean rate of late minor postoperative complications in the AC group (0.03; SD = − 0.16) was significantly lower than in the GA group (0.15; SD = 0.39) ($p = 0.05$). No significant differences between groups were found for the other subgroups of postoperative complications. Moreover, overall postoperative survival did not differ between groups ($p = 0.297$).

Conclusion These findings suggest that resection of glioblastoma using AC is associated with significantly greater extent of resection and less late minor postoperative complications as compared with craniotomy under GA without the use of surgery adjuncts. However, due to certain limitations inherent to our study design (selection bias) and the absence of the use of surgery adjuncts in the GA group, we advocate for a prospective study to further build upon this evidence and study the use of AC in glioblastoma patients.

Keywords Awake craniotomy · Glioblastoma · Extent of resection · Morbidity · Mortality

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Abbreviations

AC	Awake craniotomy
CI	Confidence interval
GA	General anesthesia
GBM	Glioblastoma multiforme
GTR	Gross total resection
EOR	Extent of resection
ICU	Intensive care unit
IDH-1	Isocitrate dehydrogenase 1
IQR	Interquartile range
ISM	Intraoperative stimulation mapping
KPS	Karnofsky Performance Status
MRI	Magnetic resonance imaging

RT	Radiotherapy
SD	Standard deviation
WHO	World Health Organization

Introduction

Glioblastomas are malignant brain tumors with an annual incidence of six per 100,000. Treatment options include surgery, along with chemo (radio)therapy. Glioblastomas are of infiltrative nature, have a relatively poor radio- and chemotherapy sensitivity, and are therefore invariably lethal. The median survival for glioblastoma multiforme (GBM) after treatment is approximately 15 months [1, 22, 25]. Due to the invasive nature of gliomas, complete resection in high-grade gliomas is not possible. Surgeons strive to resect as much of the visible part of the tumor on MRI as possible, since the extent of this resection is correlated with survival and various predictive and prognostic factors [18, 20, 21, 24]. Especially gross total resection (GTR) has been shown to increase survival in patients with high grade glioma, although at the risk of higher morbidity [14, 20].

Awake craniotomy (AC) is the technique in which the patient is awake and cooperative during the resection of the tumor [2]. This allows the surgeon, together with cortical and subcortical mapping to prevent damage to eloquent cortical and subcortical areas during resection. AC is now widely used to optimalize the extent of resection while minimalizing the risk of complications [3, 10]. Therefore, AC is preferred over craniotomy under GA in patients with low-grade glioma in (near) eloquently located tumor [10, 15, 17]. However, so far, AC has not yet been implemented routinely in high-grade glioma surgery, although preservation of quality of life in these patients should be the first concern due to the limited prognosis. Only very few studies have reported the use of AC in glioblastomas, but are only descriptive or studied in a systematic review which included also low-grade gliomas or WHO grade 3 gliomas [6, 26].

This retrospective cohort-matched study aims to determine whether AC increases the extent of resection and decreases neurological morbidity in patients with high-grade glioma as compared to resection under general anesthesia (GA).

Methods

Anesthesia, surgical procedure, and postoperative management

All patients in the AC group were extensively prepared on the procedure by the anesthetist with audiovisual media. AC-patients were sedated with propofol for craniotomy and closure and completely awake during resection of the tumor. Neuronavigation was used during all resections (AC and GA). Oxygen was provided by a nose-probe; patients were spontaneously breathing throughout the whole procedure. Local anesthesia was performed with lidocaine 1% and bupivacaine 0.25% and adrenaline 1:200.000 for the pins of the Mayfield clamp and bupivacaine 0.375% with adrenaline 1:200.000 for the surgical field. After surgical incision, craniotomy, and opening of the dura, propofol was discontinued, allowing the patient to wake up. During the resection of the tumor, standard electrocortical and subcortical stimulation and monitoring of speech and motor function were applied to resect the glioma [7]. No adjunct preoperative diagnostics such as nTMS, DTI, or fMRI were used. After resection of the tumor, the patient was sedated again with propofol until the termination of the operation.

GA patients were anesthetized with propofol, remifentanil, and rocuronium, intubated and mechanically ventilated throughout the procedure. No adjuncts to surgery were used. In patients of both groups, arterial blood pressure was measured invasively via the radial artery, and all patients received a urinary catheter. Mannitol, 200 ml 15% was given during the craniotomy period to all patients.

After suturing, all patients were brought to the post-anesthesia-high-care-unit, where they spent the first 24 h postoperatively. Morphine and paracetamol were given as postoperative analgesics routinely.

Inclusion criteria

Two cohorts were selected from a database of patients with supratentorial glioblastomas surgically treated using either AC or resection under GA at our institution. All patients were treated for glioblastoma (WHO grade IV) by senior consultant neurosurgeons between January 2005 and January 2015. Both techniques were used at the institute, but neurosurgeons not familiar with AC performed tumor resection under GA. Patients were allocated to resection under GA or AC according to the expertise of the neurosurgeon. In every case, the primary surgeon was a senior neurosurgeon with > 10 years of experience in glioma surgery, assisted by a neurosurgery resident. Allocation to treatment modality was not on the basis of the intrinsic growing nature of the tumor, such as how infiltrative or diffuse the tumor grew. In all cases, neuronavigation was used. Other adjuncts to surgery such as 5-ALA, intraoperative MRI, or ultrasound were not used because a wider spectrum of techniques used by different neurosurgeons would impede the sufficient comparison as well as the reliability of the results.

Inclusion criteria were as follows: (1) isolated GBM without evidence of multicentric or multifocal enhancement, (2) GBM location in eloquent area, (3) pathological diagnosis of glioblastoma multiforme (WHO Grade IV), (4) supratentorial lesion location, (5) preoperative KPS ≥ 70, (6) elective surgery, and (7) no crossover between groups, meaning that no individuals underwent craniotomy under both AC and GA. No patients whose craniotomy was started as AC were converted to GA during the procedure. Eloquent areas included were (1) Broca area, (2) Wernicke area, (3) primary sensory cortex/gyrus postcentralis, and (4) primary motor cortex/gyrus precentralis.

Data collection

Patient characteristics were collected from a database, and the hospital records, and presenting symptoms, neuroimaging findings, and data on (pre- and postoperative) neurological function and adjuvant treatment were documented. Preoperative KPS was assigned by the clinician at the time of evaluation and available in the chart for review in all cases. Deficits have been assessed by routine neurological examination conducted by PA's, consultants, and residents both in the ICU, neurosurgical ward, and outpatient clinic. Since this is a retrospective study, the professionals who assessed the complications were unknown of the fact that their findings would or could be used for scientific research and thus they had no direct personal interest in conducting the neurological examination and assessing the deficits. The deficits were noted in the patient records and directly exported from these records in our database. There was no room for any interpretation of the findings in any way.

The MRI characteristics that were recorded included the lesion's size, specific lobe involvement, presence of a hemorrhagic component, and the degree of mass effect. The lesion's size was before- and after surgery (residual tumor) manually calculated based on T1 with contrast MR images using the frequently used method described by (among others) Shah et al.[19] in three directions, which was approved by the neuroradiology department.

Extent of resection (EOR) as a percentage was calculated as: (preoperative tumor volume−/−postoperative tumor volume)/preoperative tumor volume. EOR was calculated based on the contrast-enhanced tumor on T1 plus gadolinium-contrast images. Operative data were reviewed for the use of awake craniotomy with motor and language mapping. Postoperative complications were classified in four categories: early minor-, early major-, late minor-, and late major complications. Classification of postoperative complications was used as described in the meta-analysis of colleagues de Witt Hamer et al[6]. Assessment of complications was done by routine neurological examinations postoperatively. For assessing the severity of a paresis, the MRC muscle scale was used, grading pareses from 0 (no contraction, paralysis) to 5 (normal power). Severe deficits involve muscle strength grades 1–3 on the MRC muscle scale, aphasia or severe dysphasia, hemianopsia, or a vegetative state. All other neurologic complications were considered less severe, including grade 4 monoparesis on the MRC scale, facial droop (central N. VII palsy), isolated cranial nerve deficit, dysnomia, somatosensory syndrome, or parietal syndrome. The distinction between early- and a late complication was 3 months postoperatively. This cutoff point is commonly considered the usual cutoff for permanency of postoperative neurologic deficits. Late complications, even minor-, are clinically important since these communicate permanent neurological complications from the surgery. Note that patients can experience multiple postoperative complications. To count more than one postoperative complication for one patient in the total number of complications, the complications have to occur independently from each other. However, if a patient experiences an early complication that becomes permanent, this will be counted both as an early complication and a late complication, since the complication has arisen from the surgery and has both short-term and long-term consequences. Transient early complications are naturally only stated as early complication as well.

Statistics: matching procedure

The number of cases meeting the inclusion criteria was 37 in de AC group and 368 in the GA group. Patient characteristics of both groups before matching are shown in Tables 1 and 2 of the Data Supplement. Because the number of patients who underwent craniotomy under GA in the same study period was disproportionately higher, a controlled matched selection of cases from the entire operative pool was performed based on the well-known strongest prognostics [3, 8]: (1) age, (2) gender, (3) preoperative KPS, (4) preoperative tumor volume, (5) tumor location, and (6) type of adjuvant treatment (none, radiotherapy, chemotherapy, chemoradiotherapy). Matching was done by a senior statistician, and case selection was blinded for primary and secondary outcomes. Propensity score matching was used to match conventional to awake patients based on the covariates gender, type of adjuvant treatment, age, preoperative KPS, preoperative tumor volume, and tumor location. Balance between the conventional and awake groups was checked with summary measures of QQplots comparing the covariates in the matched groups, and optimal results were achieved with a 1:3 matching ratio. A matching ratio of 1:3 was chosen instead of 1:1 (1) because of the rather small number of AC patients and to consequently improve precision and (2) because of the ample numbers of GA patients. "Whereas 1:1 matching may yield sufficiently precise estimates in large studies or studies with strong effects, we find that variable ratio, parallel balanced, 1:*n* nearest neighbor matching was a reasonable way to improve precision with little cost in bias" [16].

Statistics: analysis after matching

One hundred eleven cases were included in the GA cohort after matching. Patient characteristics of both groups after matching are shown in Tables 3 and 4 of the Data Supplement. After matching, differences between the AC- and GA-groups in the matched data for the primary outcomes were tested: (1) extent of resection, (2) postoperative survival, and (3) rate of postoperative complications. Analysis of the matched data set was based on non-parametrics tests, namely for the outcomes, resection, and number of complications, Mann-Whitney tests were used, whereas for median survival, the log-rank test was used. No adjustment for multiple testing has been done. The significance level was set to 5%. Due to the coded outcome-blinded matching, it was not possible to specify the postoperative complications even further beyond the current early/late and minor/major grouping after the matching procedure (i.e., motor/language, further specification of neurologic deficits). Therefore, we chose to give an even more detailed overview of the postoperative complications *before* the matching procedure, since that data is available and gives a reliable indication of the distribution of the postoperative morbidity (Table 5, Data Supplement).

Results

Baseline characteristics

The AC and GA cohorts were matched for variables that could affect the mean age, preoperative KPS, preoperative tumor volume, type of adjuvant treatment, gender, and tumor location (Table 1–4, Data Supplement). Before matching, there were significant differences in mean age ($p < 0.0001$) and preoperative KPS ($p = 0.03$) (Tables 1 and 2, Data Supplement). Preoperative tumor volume ($p = 0.23$), type of adjuvant treatment ($p = 0.61$), gender ($p = 0.73$), and tumor location ($p = 0.08$) did not differ significantly between groups (Tables 1 and 2, Data Supplement). After matching, there were no significant differences between groups in mean age ($p = 0.41$), preoperative KPS ($p = 0.64$), preoperative tumor volume ($p = 0.77$), adjuvant treatment ($p = 0.89$), gender ($p = 0.84$), or tumor location ($p = 1.00$) (Tables 3 and 4, Data Supplement). Furthermore, tumors were equally distributed between the left-right hemispheres in the groups ($p = 0.41$).

Patient outcomes

Extent of resection

Resections under AC in glioblastoma patients proved to be superior to resections under GA regarding extent of resection. The mean extent of resection in the AC group was 94.89% (SD = 10.57; IQR = 6.76), as compared to 70.30% (SD = 28.37; IQR = 44.76) in the GA group. The median extent of resection in the AC group was 100%, and 79.73% in the GA group. Table 1 and Fig. 1 provide the extent of resection per group, showing significance ($p < 0.0001$, Mann-Whitney test).

Postoperative complications

The total number of postoperative complications in 405 patients was 260, of which 176 early- and 84 late postoperative complications. Table 5 in the Data Supplement presents the distribution of postoperative complications in all patients before matching. Sixteen of the 176 early postoperative complications occurred in the AC group (rate = 0.43) and 160 in the GA group (rate = 0.41). Three of the 84 late complications occurred in the AC group (rate = 0.081), and 81 in the GA group (rate = 0.21).

Since the main objective of AC is to minimize postoperative complications while maximizing the extent of resection, the distribution and nature of the postoperative complications is of particular interest in this group. The 16 early postoperative complications in the AC group consisted of: facial droop (central N. VII palsy) ($n = 5$), aphasia ($n = 4$), monoparesis grade 4 ($n = 3$), unspecified cranial nerve deficit ($n = 2$: N. III palsy), hemiparesis ($n = 1$), and parietal syndrome ($n = 1$). The three late postoperative complications in the AC group consisted of hemiparesis ($n = 2$) and monoparesis grade 4 ($n = 1$). The AC group experienced 19 complications in total (16 early and 3 late). These 19 complications were divided over 11 patients (total, 37; rate = 0.30), while 182 of the 368 patients in the GA group experienced a complication (rate = 0.49).

Table 2 summarizes the rate of postoperative complications in both groups after matching (Mann-Whitney test). Complications were classified in four categories: early minor, early major, late minor, and late major. The mean rate of early minor postoperative complications in the AC group was 0.24 (SD = 0.64), while this was 0.22 (SD = 0.46) in the GA group ($p = 0.71$). The mean rate of early major postoperative complications in the AC group was 0.19 (SD = 0.40), as compared to 0.25 (SD = 0.48) in the GA group ($p = 0.54$). We found a significant higher rate of late minor postoperative complications in the GA group than in the AC group: 0.15 (SD = 0.39) versus 0.03 (SD = 0.16) ($p = 0.05$). The mean rate of late major postoperative complications was 0.05 (SD = 0.23), and 0.12 (SD = 0.32) in the GA group ($p = 0.27$).

Median postoperative survival

Groups were compared for postoperative survival using Kaplan-Meier curves (Fig. 2, Log-rank test). Median survival time in the AC group was not significant different than in the GA group: respectively 17 months (CI: 12.0; 36.0); as compared to 15 months (CI: 13.0; 18.0) in the GA group ($p = 0.297$; $\chi^2 = 1.1$).

Table 1 Summary statistics of percentage of tumor reduction after matching

Variable	Levels	n	$\bar{x}$	SD	$\tilde{x}$	IQR
Extent of resection (%)	General anesthesia	111	70.30	28.37	79.73	44.76
	Awake	37	94.89	10.57	100.00	6.76
$p < 0.0001$	All	148	76.45	27.27	87.67	36.31

Discussion

This matched controlled study shows that patients undergoing awake craniotomy for a single supratentorial GBM had significant greater extent of resection of their tumor compared with patients undergoing resection under GA. Moreover, the rate of late minor postoperative complications in the AC group was significant lower than in the GA group. Although a higher resection percentage, no significant increase of median survival was found after AC. This could be explained by the low amount of AC patients which remained after the matching procedure.

A point of interest in our findings is the significantly lower EOR in the GA group compared to the AC group, with simultaneously a higher rate of postoperative complications. We relate this to the fact that awake craniotomy makes 1) the surgeon braver and 2) the surgery safer. AC is about maximizing the EOR while minimizing the risk of deficits. The deficits that were particularly more observed in the GA group were dysnomia and parietal syndrome. The reason for the higher incidence of dysnomia in the GA group, namely the fact that language deficits are not as definitive. The reason for the higher incidence of parietal syndrome is the fact that the possible phenotypes of this syndrome (apraxia, neglect/spatial inattention, astereognosis, agraphaesthesia, etc.) are very complex in their pathophysiology in which not 'one eloquent area' or 'one part' of the brain dysfunctions, but in which rather a structure in a larger 'system' has been disrupted. Identification and disruption of parts of those systems are monitored by AC, which is unfortunately not possible with GA.

Current scientific literature

There is increasing evidence in the scientific literature that extensive resections are significant predictors of longer survival time in malignant glioma. However, a higher risk of morbidity has been reported before as the potential cost of pursuing gross-total resection (GTR) [14, 18, 20, 21, 24]. Surgical techniques have evolved, and the introduction of AC has proved to be a major stepping-stone in acquiring a greater extent of resection without an increased risk of morbidity. AC with cortical and subcortical stimulation has the advantage to control neurological function during brain tumor surgery and to increase the extent of resection in glioma surgery. However, AC has yet mainly been implemented for low-grade gliomas. Surgery of GBM is usually performed under general anesthesia (GA). Hence, resections are not as aggressive as possible, due the chance of seriously damaging the patient with a rather low life expectancy. Our results show that surgery with the AC technique can preserve quality of life of these patients by decreasing the risk of postoperative morbidity. Our data also shows that an increased resection with AC can attain improvement in prognosis in GBM patients, although we did not find a direct improvement in overall postoperative survival. There is extensive evidence since many years on the fact that not only the extent of resection, but especially resection percentages of >98% have been shown to increase significantly overall survival [4, 5, 11–13, 21, 23]. Also patients who previously had complete resection benefitted the most from the temozolomide regimen compared

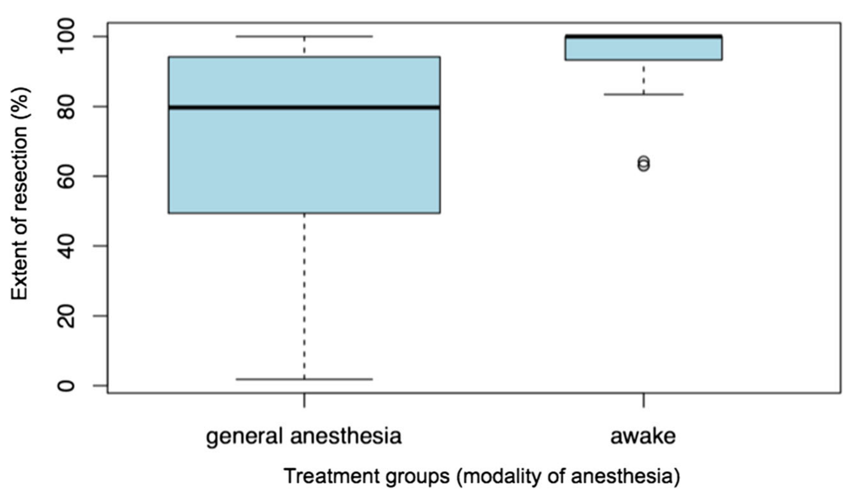

Fig. 1 Box plot of extent of resection in both groups

Table 2 Summary statistics of the number of postoperative complications after matching

Variable	Levels	n	$\bar{x}$	SD	$\tilde{x}$	IQR
Early minor	General anesthesia	111	0.22	0.46	0	0
complications	Awake	37	0.24	0.64		
$p = 0.71$	All	148	0.22	0.51	0	0
Early major	General anesthesia	111	0.25	0.48	0	0
complications	Awake	37	0.19	0.40		
$p = 0.54$	All	148	0.24	0.46	0	0
Late minor	General anesthesia	111	0.15	0.39	0	0
complications	Awake	37	0.03	0.16		
$p = 0.05$	All	148	0.12	0.35	0	0
Late major	General anesthesia	111	0.12	0.32	0	0
complications	Awake	37	0.05	0.23		
$p = 0.27$	All	148	0.10	0.30	0	0

with those who had incomplete resection (4.1 months vs. 1.8 months overall survival [21]. Thus, in addition to the survival benefit associated with maximum cytoreductive surgery such surgery seems beneficial for the efficacy of modern adjuvant treatment.

Comparison with other studies

Other studies have found similar results regarding postoperative complications and extent of resection after AC. De Witt Hamer et al.[6] conducted an extensive meta-analysis including 8091 adult patients who had surgery for supratentorial infiltrative glioma (high and low grade glioma), with or without intraoperative stimulation mapping (ISM; e.g. awake craniotomy). They found that glioma resections using ISM were associated with fewer late major neurologic deficits and more extensive resection. Although this was a mixed group of patients, these findings are entirely in line with our results in glioblastoma patients. However, they found a significant difference in late *major* neurological deficits, where we found a significant difference in late *minor* neurological deficits. Though we do not have a conclusive reason for this, we argue that the fact that the study of De Witt Hamer included patients with low-grade and high-grade glioma, which are known to have a different (infiltrative) growing pattern which might provide a framework for interpreting our results in comparison to theirs.

Yoshikawa et al.[26] conducted a study in 42 glioblastoma patients. They concluded that radical surgery with neurophysiological monitoring improved the functional outcome in glioblastoma patients. Moreover, Sacko et al.[17] prospectively studied two groups of patients with supratentorial masses ($n = 575$), comparing AC with craniotomy under GA. They found that using AC in glioma surgery proved to be superior to craniotomy under GA regarding neurological outcome and quality of resection ($p < 0.001$). The findings from these studies are in harmony with our results. Peruzzi et al.[15] add a new dimension by evaluating the length of hospital stay and impatient costs after ICU care for glioma patients who were treated with surgery under AC and GA. They concluded that patients undergoing glioma resection using AC had a significantly shorter hospital stay with reduced inpatient hospital expenses after postoperative ICU care.

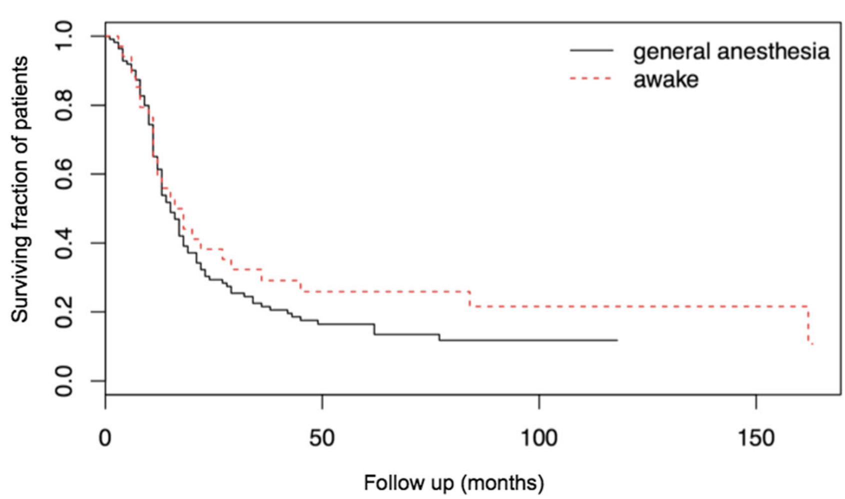

Fig. 2 Kaplan-Meier curve of postoperative survival in both groups

In contrary to current evidence, we did not find an improvement in survival in the AC group compared to the GA group, even though the extent of resection in the AC was greatly superior. We suspect this finding to be caused by the fact that a quantitative increase in extent of resection is not enough for overall survival gain. It may be very well imaginable that a greater extent of resection would lead to an increased progression-free survival/less late complications (since more volume of the tumor was resected and symptoms will stay away longer). However, there is evidence that only gross-total resection of the tumor yields a significant overall survival improvement (as stated before) [4, 5, 11–13, 23]. This means that an improvement of the mean extent of resection in our AC cohort of close to 95% as opposed to just over 70% in the GA group does not necessarily yield superior overall survival outcomes. An even greater improvement, e.g. a mean extent of resection of 97–98% would possible prove more beneficial regarding survival outcome. We do acknowledge however that studying how to push the mean EOR even further to such levels would be an excellent subject for further research (e.g., by combining AC with certain adjuncts).

Statistical analysis

For the statistical analysis, we chose the Mann Whitney *U* test (for the outcomes extent of resection and postoperative complications) and the log-rank test for survival. We would like to address the fact that the use of these statistical tests was a conscious choice, but that it would not have been the only option to analyze the results. For instance, one could argue that the use of (multivariate) regression would be appropriate to analyze the data, and we do not disagree. Our most important reason for not choosing regression is that it does not answer our research questions in the way we want them to be. For example, a regression analysis of *X, Y* with age or size as *X* and postoperative complications as *Y* gives us information about the chance of postoperative complications with a given value of *X* (age, size). This is not our research question, since we do not study the regression relationships between certain factors such as age and size on outcomes such as postoperative complications and most importantly how *Y* changes with different values of *X*. We chose log-rank and not regression because we wanted to study the difference in survival between groups and not the effect of parameter *X* on survival (*Y*), for which you would use multivariate regression analysis. Therefore, matching the factors and then analyzing them with Mann-Whitney *U* for resection%/complications and the log-rank for survival is much more suitable to answer our research question: is there a difference between these outcomes between our two (matched) groups? Regression versus Mann Whitney *U*/log-rank is an entirely valid discussion, but it depends for a whole lot on the research question: what do you want to study and which test would help you the best to answer this question? Secondly we chose our approach for statistical reasons. The Mann Whitney *U* test is a special case of the proportional odds ordinal logistic model so you could say there is no need to turn the model around to use logistic regression. Moreover, a common rule of thumb says that regression models should have ten times as many observations as parameters, which our dataset has not. Moreover, a regression analysis is less powerful than the Mann Whitney *U* test for detecting a difference in factors between groups. Because of the relatively small *n* in our dataset, we chose the more powerful approach.

Though, if one would be interested in studying the regression relationships in a large dataset between certain factors such as age and size on outcomes such as postoperative complications and most importantly how *Y* changes with different values of *X*, the use of a regression analysis would be fully warranted.

Limitations

Due to the broad spectrum of possible cofounders and bias in a study of this (retrospective) nature, we will discuss extensively the limitations of our study, how we might have minimized the risk of influence of these factors on our outcomes, and recommendations for further research to build on our results and strengthen the evidence by verifying or refining our findings.

(1) The first limitation of our study is the retrospective nature of this study with its additional concerns. As for comparing AC to GA, a strong selection bias could have been expected. It is difficult to adjust for and an inherent limitation. Though, we have tried to minimize the presence and influence of this bias, by (1) matching the groups, (2) matching with an 1:3 ratio to further increase precision, (3) the matching was outcome-blinded and done by an external person, (4) all resections were primarily done by the senior consultant (not the resident) with ample experience in resecting GBM in eloquent areas, (5) all resections had the purpose of GTR, and (6) only a very small and dedicated team works with the neurosurgeons. However, we cannot completely exclude the chance of any selection bias. Consequently, we strongly advocate for a study of prospective nature to verify our findings.

(2) We acknowledge that some postoperative complications could have been the result of postoperative ischemia. However, since the absence of routinely performed DWI sequences in our included cases, we do not have the opportunity to present data on this subject. For a more elaborate discussion about this topic, we recommend the study conducted by Gempt and colleagues in 2013 in which they present that postoperative ischemia

frequently occur in glioma patients and have an impact on postoperative neurological function [9]. Therefore, future research should take into account (1) the presence of postoperative ischemia in glioma surger and (2) use data regarding its effect to further improve the validity of the results.

(3) During resections in the GA group, no adjuncts to surgery were used such as 5-ALA or intraoperative MRI/ultrasound. We chose to operate the GA group without these adjuncts to study the effect of AC as neat as possible as compared to surgery under GA because we thought that adding these adjuncts to our analysis would blur the validity of the results rather than contribute to them. As in some practices, the use of modern adjuncts is very common and widespread; we endorse that our study reflects the net effect of AC versus GA, which may in some centers not necessarily render the extra improvement in surgical outcomes when compared to standard care.

Awake craniotomy and other surgery adjuncts

We are of the opinion that AC can still be of value when ioMRI and 5-ALA are already used, because all these techniques have a different purpose and therefore complement each other. ioMRI has as primary function to show the contrast-enhanced tumor residue intraoperatively (to let the surgeon see better). 5-ALA has the goal to push EOR by visualizing the tumor in the operative field in which the surgeon only gets unilateral dichotomous input: is it tumor or is it not? 5-ALA does not give any information about the functionality of the tissue. Thus, the function of 5-ALA is in a sense the same as ioMRI: to gain extent of resection by visualizing the remaining parts of the tumor. However, these adjuncts do not test functions intraoperatively. This is where AC has been designed for: positive or negative mapping to identify the functional areas and systems. In conclusion, AC still has value next to 5-ALA and ioMRI because these techniques do not exclude but complement each other: there is no contradiction to see better and to test function better.

Conclusions

Resection of glioblastoma as AC was in our study associated with significantly greater extent of resection and less minor late postoperative complications as compared with craniotomy under GA (without using other adjuncts to surgery than neuronavigation). No significant difference in median survival was found.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

Abbreviations chemo, chemotherapy; RT, radiotherapy; n, number; $\overline{x}$, mean; $\tilde{x}$, median; SD, standard deviation; IQR, interquartile range

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