Awake craniotomy for high-grade gliomas – a prospective cohort study in a UK tertiary- centre

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Abstract

Background:
Awake craniotomy (AC) is preferred for maximising extent of resection (EOR) in high-grade glioma (HGG) in eloquent regions without worsening neurological function. Studies from the UK reporting on AC include a heterogenous group of patients which limit the evaluation of the true impact of AC in HGG patients. This study aims to report solely the experience and outcomes of AC for HGG surgery from our centre.

Methods:
A prospective review of all patients who underwent AC for HGG from 2013–2019 were performed. Data on patient characteristics including but not limited to demographics, pre- and post-operative Karnofsky performance status (KPS), tumour location and volume, type of surgery, EOR, tumour histopathology, intra- and post-operative complications, morbidity, mortality, disease recurrence, progression-free survival (PFS) and overall survival (OS) from the time of surgery were collected.

Results:
Fifteen patients (6 males;9 females;17 surgeries) underwent AC for HGG (median age:55; range:26–73 years). Two patients underwent repeat surgeries due to disease recurrence. Median pre- and post-operative KPS score was 90 (range:80–100) and 90 (range:60–100), respectively. The EOR ranges from 60–100% with a minimum of 80% achieved in 81.3% cases. There were 15 cases of glioblastoma IDH-wildtype, CNS WHO Grade 4, 1 case of oligodendroglioma IDH-mutant 1p/19-codeleted, CNS WHO grade 3, and 1 case of Astrocytoma IDH-mutant, CNS WHO grade 3. Post-operative complications include focal seizures (17.6%), transient aphasia/dysphasia (17.6%), permanent motor deficit (11.8%), transient motor deficit (5.9%) and transient sensory disturbance(5.9%). There were no surgery-related mortality or post-operative infection. The median PFS and OS were 13 (95% CI 5–78) and 30 (95% CI 21–78) months, respectively.

Conclusion:
This is the first study in the UK to solely report outcomes of AC for HGG surgery. Our data demonstrates that AC for HGG in eloquent region is safe and feasible and provides comparable outcomes to those reported in the literature.

1. Introduction
High-grade gliomas (HGG), recognised biologically, clinically and radiologically as the more rapidly progressive and aggressive glial cell tumours, were traditionally classified as Grade III (anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic ependymoma) or IV (glioblastoma) according to the 2007 World Health Organization (WHO) classification of central nervous system (CNS) tumours[29]. However, the 2021 WHO classification (CNSS) builds on the 2016 classification and further moves towards an integrated histological and molecular diagnosis[30, 31]. This aims to better predict tumour behaviour, treatment response and prognosis[31].

In the United Kingdom (UK), the overall statistics on the incidence of HGG are unclear. In England alone, 34% of brain tumours diagnosed between 2006 and 2010 were astrocytomas, 80% of which were Grade IV (glioblastoma)[5]. In the period between 2007 and 2011, the overall national age standardised incidence of glioblastoma was 4.64/100 000/year in England[2]. As per current evidence, the UK National Institute for Health and Care Excellence (NICE) recommends that for radiologically suspected HGGs, maximal safe debulking is offered to patients as first-line treatment followed by adjuvant chemoradiotherapy[37].

The aim of surgery in HGG is maximal safe debulking which is associated with best overall prognosis while preventing post-operative neurological deficits[9]. Survival benefits have been reported in studies that achieve at least 70–80% resection of the radiologically enhancing component[6, 9, 40]. In addition, resection prevents false negatives due to limited tissue samples from biopsies and thus improves histological diagnosis to optimise adjuvant chemoradiotherapy[38]. Although gross total resection (GTR) - defined as the complete removal of radiologically enhancing tumour - is associated with greatest increase in survival[3, 21], it is often surgically challenging due to the infiltrative nature of these tumours. Maximising the extent of resection (EOR) aiming towards GTR also poses significant risks of post-operative neurological deficit, especially if the tumour is located adjacent to eloquent regions of the brain. Accordingly, onco-functional balance has been the paradigm shift in glioma surgery[10].

Awake craniotomy (AC) with intraoperative cortical and subcortical mapping is preferred for maximising EOR in eloquent region without worsening neurological functions[19]. A meta-analysis from 2019 of 53 studies comparing AC and intraoperative stimulation mapping versus resection under general anaesthesia (GA) in HGG surgery found significant improvement in surgical outcomes including longer overall survival (OS), lower post-operative complication rates and higher percentage of GTR[15]. Since then, several other meta-analyses have also demonstrated favourable outcomes for AC[4, 48]. Of note, a meta-analysis investigating outcomes of AC for resection of supratentorial glioblastoma demonstrated a GTR rate of 74.7% and a low rate of persistent neurological deficits (1.9%)[48]. Furthermore, intraoperative mapping in AC has also made resection feasible in cases where gliomas were deemed radiologically “inoperable”[42]. The UK NICE guidance for management of glioma recommends that AC is discussed with patients provided that they are unlikely to be significantly distressed by the prospect[37].

Studies to date from the UK reporting on AC include a heterogenous group of patients with low- and high-grade gliomas and/or other intracranial tumours[26, 33, 45, 46]. This limits the evaluation of surgical outcomes and the true impact of AC in HGG patients. Therefore, this study aims to report solely the
experience and outcomes of AC for HGG surgery from our centre.

2. Methods

A prospective review of all patients who underwent AC surgery for HGG at the Department of Neurosurgery in the Leeds Centre of Neurosciences, UK between 2013 and 2019 were undertaken. The study was approved by the Stroke & Neurosurgery Research Office based at the Leeds Teaching Hospitals National Health Service (NHS) Trust. Written informed consent was obtained from all included patients. All collected clinical data was analysed.

2.1 Patient selection and pre-operative planning

Patients with a confirmed brain tumour on computed-tomography (CT) and magnetic resonance imaging (MRI) were referred to the neuro-oncology multidisciplinary team (MDT) meetings for discussion. In these meetings, attended by neurosurgeons, neuroradiologists, neuro-oncologists and clinical nurse specialists (CNSs), preliminary decisions to offer AC surgery for tumour resection/debulking were made. AC was considered if the tumour was located in and/or around anatomically recognised eloquent brain areas and if the information on patient symptoms, comorbidities and functional status from the referring team supported the feasibility and appropriateness of a surgical intervention.

Following this, patients were seen in HGG clinics (most often on the same day as the MDT meeting or within a week) by the neurosurgical team with CNSs, highly specialist speech and language therapists (SLT) and physiotherapists for a holistic assessment (an essential component of the established HGG service in our centre). Standardised language assessments included but not limited to verbal fluency (semantic, phonemic and verb), object naming (Boston Naming Test), picture description (Boston Aphasia Assessment or Comprehensive Aphasia Test), sentence and paragraph auditory comprehension (Comprehensive Aphasia Test) and Pyramids and Palm Tress (PTTT) assessment of semantic access. If patients were deemed eligible for AC, the procedure was discussed further with them, specifically the benefits, risks and complications, and alternative treatment strategies. Patients were generally deemed suitable if they were in a good physical, functional, cognitive and neuropsychological state. Tumour topography was assessed with preoperative MRI (T1-weighted [pre- and post-contrast], T2-weighted and fluid-attenuated inversion recovery [FLAIR] sequences). Patients who agreed for the procedure were then scheduled for functional MRI (fMRI) and diffusion tensor imaging (DTI) to aid surgical planning of tumour resection. Informed consent for AC was obtained at this stage and confirmed on the day of surgery. Further patient review in the preoperative period by the specialist AC anaesthetic team, physiotherapists, SLT, operating surgeon(s), and neuropsychology team (especially for emotionally labile patients) was performed if required. Oral dexamethasone therapy with taper schedule and gastro-protection were also commenced for these patients until the day of surgery.

2.2 Intraoperative procedure

All patients were operated under the supervision of the senior author (GS). AC surgeries were prioritised and often listed first in the operating schedule. Patients were reviewed and accompanied to the anaesthetic room by the SLT and/or physiotherapists. They were then introduced to the surgical and anaesthetic team. Our centre used an asleep-awake-asleep or an asleep-awake-awake operating protocol. Prior to induction of anaesthesia, comfortable patient positioning on the operating table during surgery including head placement on the MAYFIELD® headrest (Integra LifeSciences, USA) was discussed with patients. Once anaesthetised, patients were positioned appropriately as discussed with them. Urinary catheterisation was not routinely undertaken to avoid catheter-related bladder discomfort due to stimulation of the trigone by the catheter balloon. Neuronavigation with Brainlab® Cranial Navigation system (Brainlab, Germany) was set up before scalp block and skin incision. Intra-operative landmarks were re-confirmed at this stage. Following craniotomy and dural opening, patients were woken for the functional mapping. Direct electrostimulation was performed using the Ojemann® bipolar electrode (Integra LifeSciences, Germany) to identify all eloquent areas which subsequently guided the EOR. If positive stimulation mapping was unsuccessful, negative mapping was adopted. SLT and physiotherapy assessment of relevant functions was carried out continuously during tumour resection. In deeper areas, subcortical testing of white matter tracts was also undertaken using the Ojemann® stimulator (Integra LifeSciences, Germany). Intraoperative seizures were managed with ice cold saline and anti-epileptic medication if needed. Intraoperative adjuncts such as 5-aminolevulinic (5-ALA) fluorescence guidance and ultrasonography were available and used at the discretion of the operating surgeon. Following tumour debulking and resection, haemostasis, dural closure, bone flap replacement and wound closure were performed. Patients were re-anaesthetised at this stage if they preferred to be asleep or were no longer tolerating the procedure whilst awake.

2.3 Postoperative procedure

Patients were observed closely after surgery for recovery at the post-anaesthesia care unit (PACU) and repatriated to standard ward beds. Post-operative MRI scans were performed within 48 hours with FUSION sequence to assess for EOR and residual tumour volume and in anticipation of adjuvant radiotherapy planning. Oral dexamethasone with taper schedule and gastro-protection was also prescribed post-operatively. Once deemed fit for discharge, follow-up visits with the neurosurgical, SLT, physiotherapy and occupational therapy teams were planned. Patients were also referred onwards to the clinical neuro-oncologists for adjuvant therapy following MDT discussion.

2.4 Data collection

Data on patient characteristics including but not limited to age, sex, symptoms, comorbidities, pre- and post-operative Karnofsky performance status (KPS) score (from clinic letters), tumour location and volume, type of surgery, and intraoperative complications were collected. EOR was calculated using the following formula: [(pre-operative tumour volume – post-operative tumour volume) / Pre-operative tumour volume] and was stated as the percentage of tumour removed[1, 41]. These individual volumes are calculated on pre-operative T1-weighted and diffusion-weighted imaging (DWI) and post-operative contrast-enhanced T1-weighted MRI images using the volumetric analysis feature (Elements SmartBrush) of Brainlab® (Brainlab, Germany). Data on tumour histology and molecular profile were also collected in addition to adjuvant therapy received, post-operative complications, deficits, mortality, disease recurrence, progression-free survival (PFS) and OS from the time of surgery.
2.5 Statistical Analysis

Data extracted were analysed using Microsoft® Excel worksheet (version 16.58) for analysis. Descriptive statistics such as count, percentages and range were performed on the worksheet. Unadjusted survival curves for PFS and OS were plotted using the Kaplan-Meier method using an R® package (version 4.2.2) in Google Colab®.

3. Results

3.1 Patient demographics and clinical features

Between 2013 and 2019, a total of 15 patients (6 male; 9 female) underwent AC for HGG with a median age of 55 years (range: 26–73). Two patients (#5 and #12) underwent repeat surgeries in the study period due to disease recurrence (making a total of 17 surgeries). The median pre-operative KPS score was 90 (range: 80–100). Patient demographics and other clinical features including presenting symptoms and comorbidities are summarised in Table 1.

Table 1
Patient demographics and clinical features

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Presentation</th>
<th>Comorbidities</th>
<th>Pre-operative KPS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>62</td>
<td>Incoordination, dysphasia, memory disturbances</td>
<td>HTN</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>60</td>
<td>Headaches, seizures, dysphasia</td>
<td>HTN; BPH; Hypercholesterolaemia</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>33</td>
<td>Headaches, dizziness, visual disturbances</td>
<td>Glioblastoma (previously operated)</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>73</td>
<td>Seizures</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>47</td>
<td>1st presentation: Dysarthria, sensory disturbances</td>
<td>-</td>
<td>90</td>
</tr>
<tr>
<td>51</td>
<td></td>
<td></td>
<td>2nd presentation: Unilateral facial weakness, sensory disturbances</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>48</td>
<td>Dysphasia, seizures, sensory disturbances</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>46</td>
<td>Seizures</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>26</td>
<td>Headaches</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>55</td>
<td>Incoordination, difficulty reading</td>
<td>HTN; DM; Hypercholesterolaemia</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>55</td>
<td>Unilateral weakness</td>
<td>Hypothyroidism</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>69</td>
<td>Dysphasia</td>
<td>-</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>54</td>
<td>1st presentation: Headaches, vomiting, dysphonia</td>
<td>Arthritis</td>
<td>90</td>
</tr>
<tr>
<td>55</td>
<td></td>
<td></td>
<td>2nd presentation: Headaches, unsteadiness, seizures</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>64</td>
<td>Seizures, tinnitus</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>54</td>
<td>Seizures, dysphasia</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>56</td>
<td>Seizures</td>
<td>Anxiety</td>
<td>100</td>
</tr>
</tbody>
</table>

M, male; F, female; BPH, benign prostatic hypertrophy; DM, diabetes mellitus; HTN, hypertension; KPS, Karnofsky Performance Status

3.2 Lesion characteristics

The tumours were located in the left hemisphere in 9 patients (9/15; 60%) and in the right hemisphere in 6 patients (6/15; 40%). The most common tumour site was the frontal lobe (9/17; 52.9%) followed by the parietal lobe (3/17; 17.6%). Five remaining cases were seen in the temporal, temporal plus insular, fronto-parietal, fronto-temporal and occipito-temporal lobes. The median tumour volume was 28.8 cm$^3$ (range: 3.37–96.1). Further details are presented in Table 2.
Table 2
Lesion characteristics, operative management and histopathology

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumour site</th>
<th>Tumour volume (cm³)</th>
<th>Surgery</th>
<th>Intraoperative complications</th>
<th>EOR (%)</th>
<th>Histology</th>
<th>Molecular profiling</th>
<th>WHO Grade</th>
<th>WHO CNS5 Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left temporal</td>
<td>96.1</td>
<td>Resection</td>
<td></td>
<td>60</td>
<td>GB</td>
<td>No      No</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>2</td>
<td>Left frontal</td>
<td>6.5</td>
<td>Resection</td>
<td></td>
<td>95</td>
<td>GB</td>
<td>No      No</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>3</td>
<td>Left frontal</td>
<td>30.4</td>
<td>Resection (Re-do with 5-ALA guidance)</td>
<td></td>
<td>100</td>
<td>Recurrent GB</td>
<td>No      No</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>4</td>
<td>Right frontal</td>
<td>11.8</td>
<td>Resection</td>
<td></td>
<td>85</td>
<td>GB</td>
<td>No      No</td>
<td>No IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>5</td>
<td>Right frontal</td>
<td>21.6</td>
<td>1st : Resection</td>
<td></td>
<td>100</td>
<td>GB</td>
<td>No      No</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td></td>
<td>Right frontal</td>
<td>51.8</td>
<td>2nd : Resection (4 years later)</td>
<td></td>
<td>95</td>
<td>GB</td>
<td>No      No</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>6</td>
<td>Left parietal</td>
<td>3.37</td>
<td>Resection</td>
<td></td>
<td>100</td>
<td>GB</td>
<td>No      No</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>7</td>
<td>Left frontal</td>
<td>85.1</td>
<td>Resection</td>
<td></td>
<td>85</td>
<td>Anaplastic OD</td>
<td>Yes Yes Yes</td>
<td>III</td>
<td>Oligodendroglioma; IDH-mutant 1p/19-codeleted, CNS WHO grade 3</td>
</tr>
<tr>
<td>8</td>
<td>Right temporal and frontal insular</td>
<td>61.7</td>
<td>Resection</td>
<td></td>
<td>90</td>
<td>Anaplastic AC</td>
<td>Yes Yes No</td>
<td>III</td>
<td>Astrocytoma IDH-mutant, CNS WHO grade 3</td>
</tr>
<tr>
<td>9</td>
<td>Left parietal</td>
<td>34.7</td>
<td>Resection</td>
<td></td>
<td>70</td>
<td>GB</td>
<td>No      No</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>10</td>
<td>Right frontal</td>
<td>45.1</td>
<td>Resection</td>
<td></td>
<td>70</td>
<td>GB</td>
<td>No      Yes</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>11</td>
<td>Left occipito-temporal</td>
<td>16.8</td>
<td>Resection</td>
<td></td>
<td>95</td>
<td>GB</td>
<td>No      Yes</td>
<td>No IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>12</td>
<td>Right fronto-temporal</td>
<td>93.3</td>
<td>1st : Resection</td>
<td></td>
<td>100</td>
<td>GB</td>
<td>No      No</td>
<td>No IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td></td>
<td>Right frontal</td>
<td>16.6</td>
<td>2nd : Resection (1 year later) Focal seizures</td>
<td></td>
<td>90</td>
<td>GB</td>
<td>No      No</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>13</td>
<td>Left fronto-parietal</td>
<td>8.1</td>
<td>Biopsy</td>
<td></td>
<td>N/A</td>
<td>Anaplastic AC</td>
<td>No      No</td>
<td>III</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>14</td>
<td>Left frontal</td>
<td>14.6</td>
<td>Resection</td>
<td></td>
<td>100</td>
<td>GB</td>
<td>No      No</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
<tr>
<td>15</td>
<td>Right parietal</td>
<td>28.8</td>
<td>Resection</td>
<td>Focal seizures</td>
<td>90</td>
<td>GB</td>
<td>No      Yes</td>
<td>IV</td>
<td>Glioblastoma IDH-wildtype, CNS WHO grade 4</td>
</tr>
</tbody>
</table>

5−ALA, 5−aminolevulinic acid; EOR, extent of resection; IDH, isocitrate dehydrogenase; MGMT, O6−methylguanine−DNA methyltransferase; WHO, World Health Organisation

3.3 Operative management
AC with tumour resection was undertaken in all but one patient (#13) where only biopsy was performed. In this patient, interhemispheric access to the frontoparietal tumour was challenging due to the presence of a significant parietal bridging vein. The patient also developed significant lower limb sensory symptoms and an intra-operative decision to not proceed further was made following discussion with the patient. In two cases (2/17, 11.8%), patients developed focal seizures during functional mapping which terminated with ice cold saline without any sequelae. In 1 patient (#3), AC with 5-ALA fluorescence-guided resection was performed since the patient had tumour recurrence following resection under GA. The EOR ranges from 60–100% of the radiologically enhancing component with a minimum of 80% EOR achieved in 81.3% of cases (13/16). Further details are presented in Table 2.

### 3.4 Histopathology

There were 14 cases of WHO Grade IV gliomas (glioblastoma) and 3 cases of WHO Grade III gliomas (2 anaplastic astrocytoma; 1 anaplastic oligodendroglia) reported as per the 2016 WHO CNS classification following the surgeries. Isocitrate dehydrogenase (IDH) gene mutation was present in 2 cases (2/17, 11.8%) while O6-methylguanine-DNA methyltransferase (MGMT) methylation was present in 5 cases (5/17, 29.4%). From the cases where 1p/19q codeletion was reported (n = 9), it was present in only 1 case (1/9; 11.1%). Following tumour reclassification using the CNS5, there were 15 cases of glioblastoma IDH-wildtype, CNS WHO Grade 4, 1 case of oligodendroglioma IDH-mutant 1p/19-codeleted, CNS WHO grade 3, and 1 case of Astrocytoma IDH-mutant, CNS WHO grade 3. Further details are presented in Table 2.

### 3.5 Postoperative outcomes

In the post-operative period, focal seizures were noted in 3 cases (3/17; 17.6%), transient aphasia/dysphasia in 3 cases (3/17; 17.6%), permanent motor deficit in 2 cases (2/17, 11.8%), transient motor deficit in 1 case (1/17; 5.9%) and transient sensory disturbance in 1 case (1/17; 5.9%). In 1 case, lumbar drain for pseudo-meningocele (patient #3) and in another, access device insertion for temporal cyst (patient #5) were further required. There were no surgery-related mortality or post-operative infection.

Adjuvant chemoradiotherapy was completed by patients in 13 cases (13/17; 76.5%) as per local protocol. However, in 2 cases (2/17, 11.8%) palliative chemotherapy was administered, and in 1 case (1/17; 5.9%) only radiotherapy was completed, due to deteriorating patient condition. In another case (1/17; 5.9%), the patient was too moribund for any adjuvant therapy.

The median post-operative KPS score was 90 (range: 60–100). A decrease in KPS score was noted in 5 cases (5/17; 29.4%). Disease recurrence was noted in 13 cases (13/16; 81.3%; 11 patients). The median PFS and OS from the time of surgery were 13 (95% CI 5–78) and 30 (95% CI 21–78) months, respectively (see Fig. 1). Further details on post-operative outcomes are presented in Table 3.
4. Discussion

It is crucial to emphasise that the 2021 CNS5 has adopted a new approach to gliomas[31]. Although histological tumour grading (WHO Grade 1–4) is still utilised, it is now entity-specific based on an integrated histological and molecular classification. In adults, diffuse gliomas are reclassified into 1) astrocytoma, IDH-mutant (Grade 2–4); 2) oligodendroglioma, IDH-mutant and 1p/19q-codeleted (Grade 2–3); and 3) glioblastoma, IDH-wildtype (Grade 4). Therefore, IDH-wildtypes diffuse astrocytic tumour, without histopathological features of glioblastoma, will be classified as glioblastoma IDH-wildtype, CNS WHO Grade 4 (i.e., “high-grade”) based on molecular profiling. In addition, the WHO CNS5 has avoided modifier terms such as “anaplastic”, previously used for “anaplastic astrocytoma (WHO Grade III)” and “anaplastic oligodendroglioma (WHO Grade III)”, rendering numerical grading of these tumours no longer straightforward. Acknowledging this, the histology and tumour grading extracted in this study period were based on classification prior to the CNS5. However, reclassification according to the CNS5 demonstrated conversion from an anaplastic astrocytoma, WHO Grade III to a glioblastoma IDH-wildtype, CNS WHO Grade 4 due to IDH mutation status in 1 case (patient #13).

We are reporting our tertiary single-centre experience on awake HGG surgery. Most studies from the UK on awake craniotomy for intracranial tumours have reported a heterogeneous cohort of patients with gliomas and metastases[26, 33, 45–47]. However, due to the aggressiveness of HGG and its contrast to low-grade glioma in tumour behaviour, it is prudent to evaluate the outcomes of surgery, awake or otherwise, for HGG separately. A meta-analysis of 37 studies (4117 patients) demonstrated a significant decrease in mortality at 1- and 2 years (P < 0.001), and likelihood of disease progression at 1 year (p < 0.001) for GTR compared to subtotal resection[3], thus indicating the advantages of safe optimisation of EOR. In another meta-analysis of 53 studies (9102 patients), AC and intraoperative stimulation mapping (ISM) was found to achieve a higher GTR percentage, a lower post-operative complication rate and a longer OS compared to craniotomy under GA for HGG resection (p < 0.001)[15]. The study authors further published a retrospective matched case-control study to evaluate AC (37 patients) versus craniotomy under GA without surgery adjuncts (111 patients) for supratentorial glioblastoma in eloquent areas and reported a greater EOR (p < 0.001)[16]. Nevertheless, due to considerable variability in the surgical approach for awake surgery between surgeons and/or centres, it is paramount to report experiences and outcomes in the field[18, 19, 22]. The AC and tumour resection for all patients in this study were performed under the supervision of an experienced senior surgeon in a similar fashion as described in methods. However, in one patient with recurrent glioblastoma encroaching on Broca's area, awake resection was performed under 5-ALA fluorescence guidance to maximise EOR – a case report was published following the surgery[8].

Similar to other centres[45, 46], AC was offered to our patients on a case-by-case basis supported by MDT discussions and patient preference. The main eligibility criterion is patient presentation with a supratentorial lesion located within/near eloquent brain regions (language and/or sensorimotor function) on...
pre-operative imaging. Hervey-Jumper et al.[23], in their retrospective review of 611 patients (55% HGG) over 14 years who underwent AC, concluded that AC can be safely performed with extremely low complication and failure rates irrespective of patient comorbidities. However, they defined a few absolute contraindications to surgery such as pre-operative uncontrolled coughing, severe dysphasia, > 25% naming errors despite a trial of preoperative dexamethasone and mannitol and hemiplegia with less than antigravity motor function (i.e., a Modified Research Council muscle strength of Grade 2 or lower) [23]. Interestingly, a Japanese study comparing awake (30 patients) versus GA surgery (30 patients) for glioblastoma resection concluded that threshold for preservation of long-term independence level post-AC were age ≤ 62 years and pre-operative KPS score ≥ 90[36]. All patients in our cohort had no or minimal comorbidities and a good functional status. Lack of clear data on patient selection from other centres in the UK also possibly imply that patients are “cherry-picked” for AC. Hence, more evidence is needed to understand the correlation between patient selection and outcomes of AC.

The evidence to support maximal safe debulking in HGG surgery is extensive[6, 25, 28, 40]. A subgroup analysis (643 patients) in a large single-centre study of 1229 patients with glioblastoma suggests that further resection of ≥ 53.21% of the surrounding FLAIR abnormality beyond the 100% contrast-enhancing resection versus less extensive resection is associated with a significant survival prolongation (median survival times: 20.7 versus 15.5 months; p < 0.001)[28]. However, surgeons are prudent in balancing maximal EOR with risks of neurological deficit. The EOR in our study ranges from 60–100% of radiologically-enhancing tumour (≥ 80% and ≥ 90% in 81.3% and 68.8% of cases, respectively), values which are comparable to other studies[15, 19]. Due to the lack of consensus on the definition of GTR[24], we reported our EOR based on percentage of tumour volume reduction post-operatively. Furthermore, studies have also reported the use of intra-operative adjuncts such as MRI, laser interstitial thermal therapy and fluorescence guidance to further optimise EOR while preserving critical structures[9, 22]. We have not utilised these except in the one case of 5-ALA-guided resection.[8]

Intraoperative stimulation-induced seizure is a known complication of AC which could lead to an AC failure (i.e., aborted mapping although tumour resection can be completed once the patient is under GA). In our cohort, we report an 11.8% rate of stimulation-induced seizures, and a 5.9% rate of AC failure (in an isolated case – patient #13). These are within the range of stimulation-induced seizure and AC failure rates of 0.21-5.5% and 0–21%, respectively published in the literature[12, 13, 20, 22, 32, 34, 39, 43, 44]. The overall postoperative complication rate from our cohort is 58.8%, higher than the reported rate in a large meta-analysis of AC and ISM in HGG surgery (13%, 95% CI 10–16). Meaningful interpretation of this can be challenging due to our small patient cohort. Nonetheless, our rates of transient and permanent neurological deficits of 29.4% and 11.8%, respectively, are comparable to other studies[11, 35]. Our median pre- and post-operative KPS score of 90 is also consistent with other institutional experiences[14, 27]. This is also true for our 0% infection rate and 30-day mortality[23, 26].

There is discrepancy in the reported studies on survival following AC for HGG. Gerritsen et al.[16], reported a significantly longer median OS in AC plus ISM (210 patients; 16.9 months) versus GA craniotomy (4390 patients; 12.0 months) for HGG surgery in their meta-analysis (p < 0.001). However, this is a meta-analysis of observational/retrospective studies as the study authors have claimed. A retrospective multicentre study (891 patients) comparing AC (21%) and GA (79%) for HGG surgery found no difference in median PFS or median OS[7]. The recent multi-centre cohort study (GLIOMAP) by Gerritsen et al.[17] on the effect of AC in glioblastoma in eloquent areas reported longer median PFS and median OS in AC versus asleep for cohort younger than 70 years (PFS: 9.3 months [95% CI 8.0–12.0] versus 7.5 months [6.5–9.0]; p = 0.0061; OS: 19.5 months [95% CI 16.0–31.0] versus 15.0 months [13.0–17.0]; p < 0.0001) and with a pre-operative KPS score of 90–100 (PFS: 10.0 months [9.0–13.0] versus 8.0 months [7.0–9.0]; p = 0.0010; OS: 19.0 months [16.0–31.0] versus 14.5 months [13.0–16.5]; p = 0.00058). The median PFS and median OS of 13 and 30 months, respectively in our study were also comparable to the numbers reported in literature[7, 16, 17].

There are a few limitations to this study such as the small sample size, selection bias and confounding. In this case, we focused solely on the surgical outcomes of AC for HGG surgery in a single centre. Secondly, the considerable variability in various facets of AC such as anaesthetic technique, mapping protocols, use of intraoperative adjuncts and intraoperative decision-making process cannot be overstated and makes comparison challenging. There is also lack of well-defined patient selection criteria. Finally, the small sample size limited further analyses of the impact of EOR, pre- and post-operative KPS, adjuvant therapy and recurrence on PFS and OS.

5. Conclusions

This is the first study in the UK to report outcomes of AC for HGG surgery alone. Our study demonstrates that AC for HGG is safe and feasible and provides comparable functional outcomes to those reported in the literature. Our holistic HGG service and MDT approach to patient selection and surgical planning enable a gold-standard surgical treatment to be offered to these patients, thus limiting the need for additional biopsies. However, larger studies with a clearly defined patient selection criteria, methodology and outcome measures are needed to establish the impact of AC in HGG surgery.

Abbreviations

5-aminolevulinic (5-ALA)
Awake craniotomy (AC)
Central nervous system (CNS)
Clinical nurse specialist (CNS)
Computed tomography (CT)
Diffusion tensor imaging (DTI)
Declarations

Ethics declaration

Ethics approval

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Stroke & Neurosurgery Research Office based at the Leeds Teaching Hospitals National Health Service (NHS) Trust, Leeds, United Kingdom.

Consent to participate

Written informed consent was obtained from all included patients or their next of kin if patient lacked the capacity to consent.

Conflict of interest

The authors declare that they have no conflict of interest.

References


Figures
Figure 1

Kaplan-Meier estimates of a) progression free survival (PFS) and b) overall survival (OS)