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The SAFE-trial

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The SAFE-trial: Safe surgery for glioblastoma multiforme: Awake craniotomy versus surgery under general anesthesia. Study protocol for a multicenter prospective randomized controlled trial

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ABSTRACT

Background: Surgery of GBM nowadays is usually performed under general anesthesia (GA) and resections are often not as aggressive as possible, due to the chance of seriously damaging the patient with a rather low life expectancy. A surgical technique optimizing resection of the tumor in eloquent areas but preventing neurological deficits is necessary to improve survival and quality of life in these patients. Awake craniotomy (AC) with the use of cortical and subcortical stimulation has been widely implemented for low-grade glioma resections (LGG), but not yet for GBM. AC has shown to increase resection percentage and preserve quality of life in LGG and could thus be of important value in GBM surgery.

Methods/design: This study is a prospective, multicenter, randomized controlled trial (RCT). Consecutive patients with a glioblastoma in or near eloquent areas (Sawaya grading II/III) will be 1:1 randomized to awake craniotomy or craniotomy under general anesthesia. 246 patients will be included in neurosurgical centers in the Netherlands and Belgium. Primary end-points are: 1) Postoperative neurological morbidity and 2) Proportion of patients with gross-total resections. Secondary end-points are: 1) Health-related quality of life; 2) Progression-free survival (PFS); 3) Overall survival (OS) and 4) Frequency and severity of Serious Adverse Effects in each group. Also, a cost-benefit analysis will be performed. All patients will receive standard adjuvant treatment with concomitant chemoradiotherapy.

Discussion: This RCT should demonstrate whether AC is superior to craniotomy under GA on neurological morbidity, extent of resection and survival for glioblastoma resections in or near eloquent areas.

Trial registration: Clinicaltrials.gov: NCT03861299
Netherlands Trial Register (NTR): NL7589

Abbreviations: 5-ALA, 5-Aminolevulinic Acid; AC, Awake craniotomy; AE, Adverse Event; CI, Confidence Interval; CTC, Clinical Trial Center; DTI, Diffusion Tensor Imaging; EMC, Erasmus Medical Center; ETZ, Elisabeth-TweeSteden Hospital; fMRI, Functional Magnetic Resonance Imaging; GA, General Anesthesia; GCP, Good Clinical Practice; HMC, Haaglanden Medical Center; HRQoL, Health-related Quality of Life; ISM, Intraoperative Stimulation Mapping; KPS, Karnofsky Performance Score; LGG, Low-grade glioma; METC, Medical Ethics Committee; NIHSS, National Institute of Health Stroke Scale; NTR, Dutch Trial Register; OS, Overall survival; PACU, Post-Anesthesia Care Unit; PFS, Progression-free survival; UMCG, University Medical Center Groningen; UZG, University Hospital Gent; WHO, World Health Organization

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1. Background

Glioblastoma multiforme (GBM) or astrocytomas grade IV (WHO) are devastating tumors with one of the worst prognosis in oncology. The median survival after surgery and treatment with chemo and radiotherapy ranges from 12 to 15 months and no curative therapy is currently available [1,2]. The annual incidence is approximately 5 per 100,000 with a prevalence of 800–1000 cases each year in the Netherlands [3]. Patients usually present with speech difficulties, unilateral paresis in arms and/or legs, headache, cognitive problems or epilepsy [4]. Multiple studies show that extent of resection of the tumor improves survival in patients with GBM [5–12]. Further analyses showed that patients who previously had complete resection derived the most benefit from the temozolomide regimen compared with those who had had incomplete resection [13]. Thus, in addition to the survival benefit associated with maximum cytoreductive surgery such surgery seems essential for the efficacy of modern adjuvant treatment.

> 50% of GBMs are located near or in eloquent areas of the brain. Eloquent areas are important areas within the brain were speech and/or motor functions are located [4]. Damaging these areas during surgery has serious impact on the quality of life and could even exclude patients from after treatment with radio- and chemotherapy. The surgeon cannot identify these eloquent areas during resections under general anesthesia (GA). Therefore, when resecting GBMs in these areas, they are usually not operated as aggressive as possible, due the chance of seriously damaging the patient with a rather low life expectancy [1,7,9–12,14]. However, partial or subtotal resections will benefit less from radio- and chemotherapy as total resections [5–12]. A surgical technique optimizing resection of the tumor in eloquent areas but preventing neurological deficits is necessary to improve survival and maintain quality of life in these patients.

Awake craniotomy (AC) is the technique in which the patient is awake and cooperative during the resection of the tumor [14]. This allows the surgeon, together with cortical and subcortical mapping to prevent damage to eloquent cortical and subcortical areas during resection [15,16]. AC has shown to increase resection percentage and preserve quality of life in low-grade glioma (LGG) and could be of important value in the surgery of GBM [15,17,18]. Awake craniotomy could also optimize the extent of resection and therefore improve survival in these patients [15,17–25]. Only very few studies have reported the use of AC in GBM [26,27]. We recently showed in a meta-analysis and a retrospective matched case-control study that patients with GBM operated with AC had less early postoperative neurological morbidity and significantly higher percentage of total resection [28,29]. AC could thus be of high value in the surgical treatment of GBM in eloquent areas. Therefore, we designed the SAFE-trial: a multicenter randomized controlled study which will compare AC with craniotomy under GA in patients with GBM.

2. Methods/design

2.1. Trial design

This is a prospective, multicenter, 2-arm randomized controlled trial (RCT). Eligible patients are randomized to AC (intervention arm) or craniotomy under GA (control arm) (Fig. 1).

2.2. Study objectives

The primary study objective is to assess the safety and efficacy of AC versus GA in patients with GBM in eloquent areas as expressed by NIHSS scores and extent of resection on MRI.

Secondary study objectives are to assess the postoperative quality of life and survival of AC versus GA as expressed by health-related quality of life (HRQoL, using the QLQ-C30, QLQ-BN20 and EQ-5D questionnaires) and (progression-free) survival (PFS/OS).

2.3. Study setting and participants

Patients will be recruited for the study from the neurosurgical or neurological outpatient clinic or through referral from general hospitals of the five participating neurosurgical hospitals. The four Dutch participating neurosurgical hospitals are Erasmus Medical Center (EMC) Rotterdam, Haaglanden Medical Center (HMC) The Hague, Elisabeth-Tweesteden Hospital (ETZ) Tilburg and University Medical Center Groningen (UMCG). The participating Belgian hospital is the University Hospital Gent (UZG). The study is open to additional participating neurosurgical centers. We expect to complete patient enrollment in 4 years. The estimated duration of the study (including follow-up) will be 5 years.

2.4. Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Age ≥ 18 years and ≤ 90 years
2. Tumor diagnosed as glioblastoma multiforme (GBM) on MRI with a distinct ring-like pattern of contrast enhancement with thick irregular walls and a core area reduced signal suggestive of tumour necrosis as assessed by the surgeon
3. Tumors situated in or near eloquent areas; motor cortex, sensory cortex, subcortical pyramidal tract or speech areas as indicated on MRI (Sawaya Grading II and II)
4. The tumor is suitable for resection with both modalities (according to neurosurgeon)
5. Karnofsky performance scale 80 or more
6. Written informed consent

2.5. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Tumors of the cerebellum, brain stem or midline
2. Multifocal contrast enhancing lesions
3. Substantial non-contrast enhancing tumor areas suggesting low grade gliomas with malignant transformation
4. Medical reasons precluding MRI (e.g. certain pacemakers)
5. Inability to give informed consent (e.g. severe language barrier)
6. Psychiatric history
7. Previous brain tumour surgery
8. Previous low-grade glioma.
9. Second primary malignancy within the past 5 years (with the exception of adequately treated in situ carcinoma of any organ or basal cell carcinoma of the skin).
10. Severe aphasia or dysphasia

2.6. Interventions

2.6.1. Craniotomy under general anaesthesia

On the evening before surgery 1.5–2.0 mg lorazepam is administered for anxiolysis.

60 min. Before anaesthesia induction the patient receives 1 g paracetamol p.o. and 7.5–15 mg midazolam p.o. if requested for sedation. 1 g cefazoline is given iv. for antibiotic prophylaxis before anaesthesia induction.

General anaesthesia is induced intravenously with fentanyl 0.25–0.5 mg, propofol 100–200 mg and cis-atracurium 10–20 mg. After induction of anaesthesia, patient is orotracheally intubated and mechanical ventilation is applied. Respiratory rate and tidal volume are adjusted to keep the patient normocapnic.

An arterial line, central venous catheter (v. basilica), and urinary

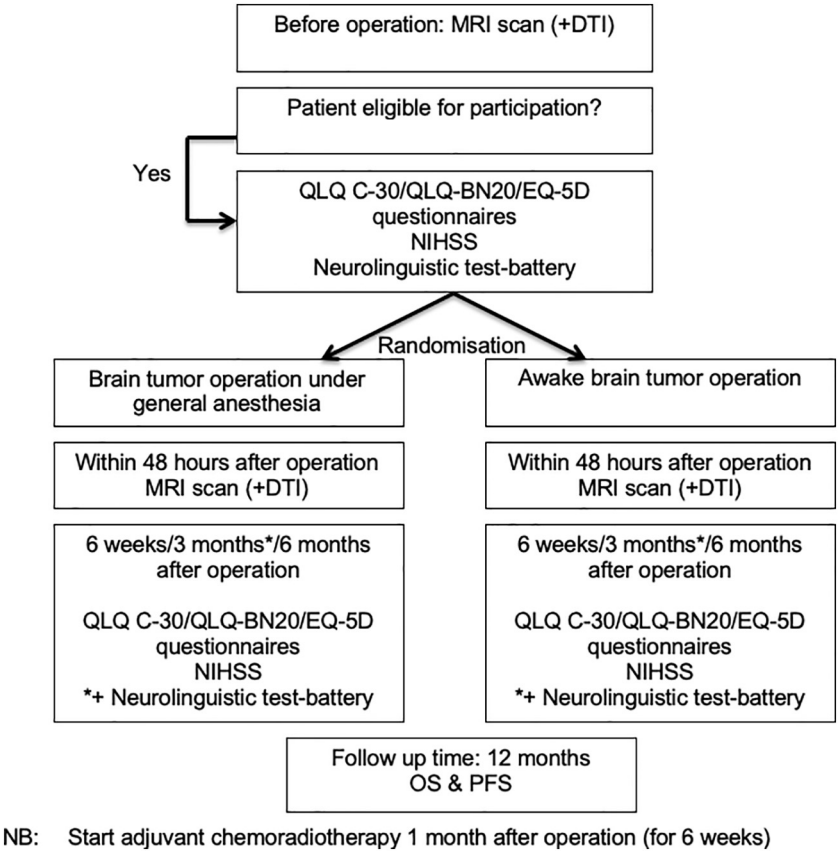

Fig. 1. Study flowchart.

catheter are inserted. Anaesthesia is maintained with propofol (up to 10 mg/kg/h) and remifentanil (0.5–2 μg/kg/min). isoflurane (up to 1 MAC) and clonidine (1–2 μg/kg) may be added for maintenance, if necessary. The fluid management is aiming for normovolemia. 0.9% saline solution and balanced crystalloids are used for maintenance, in case of blood loss > 300 ml, HAES 130/0.4 solution will be given.

Temperature management is aiming for normothermia, warm-air blankets and warmed infusion lines are used. Arterial blood gas analysis is performed at the beginning of the procedure and repeated, if necessary. Electrolytes are controlled and substituted and hyperglycemia will be treated with insulin, if necessary.

The anesthetized patient is positioned on the table. Local infiltration of the scalp is performed with 20 ml lidocaine 1% with adrenaline 1:200.000 to reduce bleeding. The insertion points of the Mayfield clamp are not infiltrated with local anaesthetics.

Trephination and tumour resection are performed without any additional neuro-psychological monitoring, guided by STEALTH-neuronavigation. At the end of the procedure all anaesthetics are stopped and patient is brought to the Post Anaesthesia Care Unit (PACU). Detubation of the patient is performed as early as possible, if patient fulfils the detubation criteria (> 36 C body temperature, stable hemodynamics, sufficient spontaneous ventilation, adequate response to verbal orders). Postoperative analgesia is provided with Paracetamol i.v. or p.o. 1 g up to 4 dd and morphine 7.5 mg s.c. up to 4 dd, if necessary. At the PACU the patient is hemodynamically and neurologically monitored for 24 h.

2.6.2. Awake craniotomy under local anaesthesia; procedure:

On the evening before surgery 1.5–2.0 mg lorazepam is administered for anxiolysis. Thirty minutes before anaesthesia induction an intramuscular injection of 7.5 mg piritramide and 25 mg promethazine is given. The patient is sedated with a bolus injection of propofol (0.5–1 $mg.kg^{-1}$) and kept sedated with a propofol infusion pump (mean: 4 $mg.kg^{-1}.h^{-1}$). An arterial line, central venous catheter, and urinary catheter are inserted. The patient is awakened and positioned on the table. At this point local anaesthesia for the fixation of the head in the Mayfield clamp and the surgical field is provided with a mixture of 10 ml lidocaine 2% with 10 ml bupivacaine 0.5% plus adrenaline 1:200,000 for the Mayfield clamp and up to 40 ml bupivacaine 0.375% with adrenaline 1:200,000 for the surgical field.

After positioning, clamp fixation, and surgical field infiltration, patients are sedated again for the trephination until the dura mater is opened, after local application of some drops of local anaesthetics. Propofol sedation is stopped after opening of the dura, with the patient awakening with as few external stimuli as possible. Cortical stimulation is performed with a bipolar electrical stimulator. The distance between both poles is 5 mm, and stimulation is performed by placing this bipolar pincet directly on the cortical surface and stimulating with increasing electrical biphasic currents of 2–12 mA (pulse frequency 60 Hz, single pulse phase duration of 100 microsec.) until motor or speech arrest is observed. For motor mapping a 2-s train and for speech mapping a 5-s train is used, respectively.

The Boston naming test and repetition of words is done in cooperation with a neuropsychologist/linguist, who will inform the neurosurgeon of any kind of speech arrest or dysarthria. The difference between these is not always clear, but can be distinguished from involuntary muscle contraction affecting speech. When localizing the motor and sensory cortex, the patient is asked to report any unintended movement or sensation in extremities or face.

Functional cortical areas are marked with a number. After completion of cortical mapping, a resection of the tumour is performed as radical as possible using an ultrasonic aspirator and suction tube, while sparing these functional areas. When the tumour margins or white matter is encountered or when on regular neuronavigation the eloquent

white matter tracts are thought to be in close proximity, subcortical stimulation (biphasic currents of 8–16 mA, pulse frequency 60 Hz, single pulse phase duration of 100 microsec., 2-s train) is performed to localize functional tracts. If subcortical tracts are identified, resection is stopped. During the resection of the lesion close to an eloquent area, the patient is involved in a continuous dialogue with the neuropsychologist. That way the neurosurgeon has 'online'-control of these eloquent areas. In case of beginning disturbances of communication or of motor or sensory sensations the resection is cessated immediately. When, due to stimulation, an epileptic seizure occurs, this is stopped by administering some drops of iced saline on the just stimulated cortical area. Although not performed at our institution, continuous corticography may be used to monitor after discharge potentials to identify subclinical seizure activity. After resection of the tumour a final neurological examination is performed. During closure of the surgical field the patient is sedated with propofol again. After wound closure and dressing, sedation is stopped. The awake patient is transferred to the post-anaesthesia care unit, where the patient is hemodynamically and neurologically monitored for 24 h.

2.6.2.1. Intraoperative imaging. The use of fMRI, DTI (Diffusion Tensor Imaging), ultrasound or 5-ALA is allowed to be used in both groups on the surgeons indication.

2.7. Outcomes

2.7.1. Primary outcome measures

The primary outcomes are 1) the proportion of patients with ≥ 1 point deterioration on the NIHSS (National Institute of Health Stroke Scale) at 6 weeks postoperatively; and 2) the proportion of patients without residual contrast-enhancing tumour on the 48 h postoperative MRI ($\leq 0.175\ cm^3$ residual tumor).

2.7.2. Secondary outcome measures

The secondary outcomes are 1) health-realted quality of life (HRQoL) at 6 weeks, 3- and 6 months postoperatively (using the QLQ-C30, QLQ-BN20 and EQ-5D questionnaires); 2) progression-free survival (PFS) at 12 months defined as time from diagnosis to disease progression (occurrence of a new tumor lesions with a volume $> 0.175\ cm^3$, or an increase in residual tumor volume of $> 25\%$) or death, whichever comes first; 3) overall survival (OS) at 12 months defined as time from diagnosis to death from any cause; 4) frequency and severity of (Serious) Adverse Events in each group (e.g. infections, intracerebral hemorrhage, epilepsy, aphasia and paresis/paralysis in extremities). Aphasia will be determined with a short neurolinguistic test-battery before and at 3 months after operation in each group including: Aphasia Bedside Check (ABC), shortened Token Test, verbal fluency (category and letter), picture description and the Montreal Cognitive Assessment (MOCA).

2.8. Randomization

Each participating center will randomize eligible and willing patients through the webbased clinical database and randomization application ALEA. The Clinical Trial Centre (CTC) of the Erasmus MC will build the randomization application by use of a dynamic allocation algorithm (minimization), in which patients are allocated to keep the imbalance between treatment groups to a minimum at every stage of recruitment within the covariates age (≤ 55 years *vs* > 55 years), Karnofsky performance scale (80–90 *vs* > 90), and left or right hemisphere. Treatment allocation and allocated subject number will be shown immediately on screen and will in addition automatically be emailed to local investigators and other study personnel.

2.9. Study procedures: Clinical evaluations and follow up

1. Baseline

1) Assessment of baseline symptom(s) and medical history
2) Full neurological examination (NIHSS)
3) Questionnaires: EORTC QLQ-BN20, EORTC QLQ-C30 and EQ-5D
4) Neurolinguistic test-battery (ABC, Shortened Token Test, verbal fluency, picture description, MOCA).

NIHSS

The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke, but has been used extensively for outcome in glioma surgery because of the lack of such scale for neuro-oncologic purposes and has been validated. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

QLQ-C30

The European organisation for research and treatment of cancer (EORTC) developed the QLQ-C30 questionnaire for cancer patients, and the disease specific QLQ- BN20, specifically developed and validated for patients with brain tumor. Both tools have been tested and validated in clinical trials. The 50 questions in both questionnaires together take 20 min to complete.

The EORTC QLQ-C30 measures functioning scales - physical, role, emotional, cognitive and social; three symptom scales - fatigue, nausea/vomiting and pain; six single item scales - dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact; and the overall HRQOL scale.

QLQ-BN20

The EORTC QLQ-BN20 is designed for patients undergoing chemotherapy or radiotherapy and includes 20 items assessing visual disorders, motor dysfunction, communication deficit, various disease symptoms (e.g. headaches and seizures), treatment toxicities (e.g. hair loss), and future uncertainty. Both items are scaled, scored and transformed to a linear scale (0–100). Differences ≥ 10 points are classified as clinically meaningful changes in a HRQL parameter.)

EQ-5D

EQ-5D is a standardized instrument for measuring generic health status. The health status measured with EQ-5D is used for estimating preference weight for that health status, then by combining the weight with time, quality-adjusted life year (QALY) can be computed. QALYs gained is used as an outcome in cost-utility analysis which is a type of economic evaluation that compares the benefit and cost of health care programs or interventions.

Aphasia Bedside Check (ABC)

ABC is a short screening test to detect aphasic disturbances at language comprehension and language production level at the main linguistic levels. It consists of 14 items in total. The cut-off score for signs of aphasia is ≤ 12.

Shortened Token Test

The shortened Token Test is a test for language comprehension and for the severity of a language disorder. The patient is asked to point and to manipulate geometric forms on verbal commands. It consists of 36 items. The cut-off score is 29.5.

Verbal fluency (category and letter)

Category and letter fluency are tests to assess flexibility of verbal semantic and phonological thought processing, semantic memory and concept generation. The patients is asked to produce words of a given category (animals, professions) or beginning with a given letter (D, A, T) within a limited time span.

Picture description

This is a subtest from the CAT-NL to assess semi-spontaneous speech in an oral and written way (5 min each condition). Scoring can be done according to the manual or more thoroughly according to the variables mentioned by Vandenborre et al.

Montreal Cognitive Assessment (MOCA)

The MOCA is a cognitive screening test to detect mild impairments across several cognitive domains; attention, verbal memory, language, visuo-constructive skills, conceptual thought, calculation and orientation. The total score is 30, the cut-off score is ≤ 26.

2. Preoperatively

1) MRI-brain-navigation with Gd-contrast (standard procedure).
2) Diffusion-tract imaging (DTI)

3. Postoperatively

1) MRI-brain with Gd-contrast within 48 h postoperatively
   a. Extent of resection will be assessed by two independent neuroradiologists
2) Description of presenting symptom(s) at day 1–2-3- postoperatively
3) Full neurological examination at day 1–2-3 postoperatively

4. 6 weeks follow up after surgery

1) Description of presenting symptom(s)
2) Full neurological examination (NIHSS)
3) Questionnaires: EORTC QLQ-BN20, EORTC QLQ-C30 and EQ-5D

5. 3 months follow up after surgery

1) Description of presenting symptom(s)
2) Full neurological examination (NIHSS)
3) Questionnaires: EORTC QLQ-BN20, EORTC QLQ-C30 and EQ-5D
4) MRI-brain with Gd-contrast
5) Neurolinguistic test-battery (ABC, Shortened Token Test, verbal fluency, picture description, MOCA)

6. 6 months follow up after surgery

1) Description of presenting symptom(s)
2) Full neurological examination (NIHSS)
3) Questionnaires: EORTC QLQ-BN20, EORTC QLQ-C30 and EQ-5D
4) MRI-brain with Gd-contrast

7. 12 months follow up after surgery.

1) Overall survival (as assessed by digital medical records of the hospital)
2) Progression-free survival (as assessed by routine MRI)

2.10. Sample size

This study has two primary endpoints. In order to guarantee that the overall type I error rate does not exceed 5%, we apply a weighted Bonferroni correction for multiple testing. The sample size calculations that follow take that into account.

For the first primary endpoint, proportion of patients with NIHSS deterioration at 6 weeks post-surgery, we assume a deterioration rate of 15% in the control group, and 3% in the experimental group. A two-sample test for proportions with continuity correction requires 222 patients (111 per arm) in total in order to detect the above mentioned difference of 12% with 80% power at a 4% significance level.

For the second primary endpoint, proportion of patients without residual contrast-enhancing tumor on postoperative MRI, we assume a success rate of 25% in the control group, and 50% in the experimental group. A two-sample test for proportions with continuity correction requires 188 patients (94 per arm) in total in order to detect the above mentioned difference of 25% with 80% power at a 1% significance level.

In order to power the study for both primary endpoints, we should include the larger required number of patients, i.e. 222. A total of 222 eligible and evaluable patients allow the difference of 25% in proportion of patients without residual tumor to be detected with 88% power. Taking into account possible ineligibility and withdrawal of consent (we estimate this at 10%), a total of 246 patients will be included.

2.11. Data collection

All patient data is collected in the electronic data software ALEA (FormsVision B.V., Abcoude, The Netherlands). This software allows built-in logical checks and validations to promote data quality. Data entry is performed by the study coordinator or locally by trained research nurses and physicians.

2.12. Data analysis

All analyses will be according the intention to treat principle, restricted to eligible patients. That means that patients will be analysed according to the group they were randomized to, irrespective of the type of surgery actually received.

Patients initially registered but considered ineligible afterwards based on the histological analysis on tissue extracted during surgery, will be excluded from all analyses.

It is not expected that many patients will refuse AC after being randomized for this group. Yet these patients will not be excluded from the analyses, as suggested by the intention to treat principle. However, if this would have happened for some patients, a sensitivity analysis will be performed on the basis of the treatment actually received, i.e. per protocol analysis.

2.12.1. Primary study parameters

The primary endpoints will be analyzed using multivariate logistic regression, where treatment group effect will be corrected for minimization factors age group (≤ 55 years vs > 55 years), Karnofsky performance scale (80–90 vs > 90), and left or right hemisphere (presented in order of decreasing prognostic value).

As the frequency of NIHSS deterioration is expected to be relatively low, we may not be able to correct for all randomization stratification factors as mentioned above. We will be including a stratification factor in the primary analysis model with each 10 observed events using the order of prognostic value as mentioned in the paragraph above, where the first 10 events will be used to estimate the effect of the arm. This rule will be applied in case < 40 patients in total develop NIHSS deterioration.

In the so constructed multivariate logistic regression model the treatment arm effect will be tested at 4% significance level.

The primary analysis of proportion of patients without residual contrast-enhancing tumour consist of a multivariate logistic regression, where arm effect is corrected for all minimization factors. In this model the group effect will be tested at 1% significance level. Manual segmentation will be performed on axial T1 MRI contrast enhanced slices to measure tumor volume. A determination of volumes will be calculated blinded for the treatment group.

2.12.2. Secondary study parameters

Health related quality of life as measured with the QLQ-C30, QLQ-BN20, and EQ5D will be summarized cross-sectionally at 6 weeks, 3 and 6 months after surgery, as well as change from baseline. The difference between treatment arms will be described as well.

The Kaplan-Meier method will be used to estimate PFS and OS proportions per treatment group at appropriate time points, while the

Greenwood estimate of the standard error will be used to construct the corresponding 95% CI. Multivariate Cox proportional hazards models will be build for PFS and OS where treatment group effect will be corrected for minization factors age group ($\leq$55 years vs > 55 years), Karnofsky performance scale (80–90 vs > 90), and left or right hemisphere. Additionally, competing risk analysis will be used to calculate cumulative incidence of PFS (with competing risks progression/relapse and death without progression/relapse which add up to 100% at every time point). SAE's in both groups will be described.

2.13. Study monitoring

The Clinical Trial Center of the Erasmus Medical Center will perform on-site monitoring visits to verify that the rights and well-being of patients are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s). Monitoring visits will take place according to the study specific monitoring plan.

2.14. Adverse events (AEs) and serious adverse events (SAEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to neurosurgery. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded from start of surgery until 6 weeks after surgery. Serious adverse events are any untoward medical occurrence or effect that results in death; is life-threatening (at the time of the event); requires hospitalization or prolongation of existing inpatients' hospitalization; results in persistent or significant disability or incapacity or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention, but could have been based upon appropriate judgement by the investigator. An elective hospital admission will not be considered as a serious adverse event. Most of the (serious) adverse effects of treatments (awake surgery or surgery under generalised anaesthesia) will be mainly related to the surgery: post operative pain, nausea and anaemia (in case of massive blood loss), Infections, intracranial haemorrhage, epilepsy, aphasia, paresis/paralysis in arms or/and legs.

The neurological morbidity is under investigation in this trial and well known risk / complications of the craniotomy and can be attributed to the nature of the operation. Neurosurgical clinics are well adapted to prevent and treat such events. Therefore, the Local Investigator should report only Serious Adverse Events expedited (within 24 h of first knowledge) that occur from start of surgery until 6 weeks after surgery and that result in death or are life threatening.

The sponsor will re-assess the expectedness and report fatal and life threatening SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge, followed by a period of maximum of 8 days to complete the initial preliminary report.

2.15. Publication of results

Trial results will be published in an international journal, communicated to neurological and neurosurgical associations and presented at (inter)national congresses.

3. Discussion

Neurosurgeons have a daunting task: resecting the tumor with an extent as great as possible, while simultaneously minimizing the risk for postoperative complications and especially neurological morbidity. AC can significantly contribute to this goal by preserving the quality of life of these patients (and decreasing the risk of postoperative morbidity) when operating in eloquent areas, while increasing extent of resection (and maximizing postoperative survival).

With AC, the neurosurgeon uses electrocortical and subcortical mapping to differ eloquent brain tissue from brain- or tumor tissue that is safe to resect. To date, AC is used in particular for the resection of low-grade gliomas because of the usually near-eloquent location of these tumors and many studies have shown that AC greatly increases resection percentage while preserving QoL in low-grade glioma (LGG) [15,30]. Only very few studies have evaluated the use of these techniques in glioblastomas [15–18,26,27]. Arguably one of the more extensive studies was conducted by Sacko et al., who prospectively studied two groups of patients with supratentorial masses ($n = 575$), comparing AC with craniotomy under GA [18]. They found that using AC in glioma surgery proved to be superior to craniotomy under GA regarding neurological outcome and quality of resection ($p < .001$). Other substantial evidence came from the group of De Witt Hamer et al., who conducted an extensive meta-analysis including 8091 adult patients who had surgery for supratentorial infiltrative glioma (high- and low-grade glioma), with or without intra-operative stimulation mapping (ISM; e.g. awake craniotomy) [26]. They found that glioma resections using ISM were associated with fewer late major neurologic deficits and more extensive resection. However, the evidence from these studies is lacking the quality to substantiate the use of AC as standard treatment in glioblastoma surgery: the investigated groups are very small, mixed with II and –III tumors and lacking robust statistical analyses to correct for co-factors. Recently, more robust evidence regarding the use of AC in glioblastoma patients was published. Researchers from the Erasmus Medical Center conducted a retrospective matched case-control study including 148 patients undergoing craniotomy for glioblastoma [29]. They found that resection of glioblastoma using AC as 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. Moreover, a recent meta-analysis that specifically aimed to summarize the available research evidence on the use of AC in glioblastoma was conducted [28]. The analysis included 53 studies and 9102 patients. This paper proved substantial evidence that AC yielded superior outcomes in glioblastoma resections as compared to GA: the overall postoperative median survival in the AC group was significantly longer (16.87 versus 12.04 months; $p < .001$) and the postoperative complication rate was significantly lower (0.13 versus 0.21; $p < .001$). Furthermore, extent of resection and preoperative patient KPS were indicated as prognostic factors, whereas patient KPS and involvement of eloquent areas were identified as predictive factors.

Overall, AC has been thoroughly demonstrated as an effective surgical technique in the current literature for low-grade glioma. AC is showing promising results as a technique used for glioblastoma resections, in particular in eloquent areas. Confirmation of these results is essential by means of RCTs.

3.1. Trial status

This trial started on April 1st, 2019. The study is open to additional participating neurosurgical centers.

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Authors' contributions

AV designed the study, obtained funding, wrote the study protocol and is end-responsible for the implementation and organization of the study in all participating centers. JG wrote the study protocol and is

responsible for the implementation and organization of the study in all participating centers and the conduct of the database. CD contributed to the design of the study. EO contributed to the design of the study and will perform the statistical analyses. MK contributed to the design for the study and is, together with CD, RD and AV responsible for the local conduct of the study at EMC. MG contributed to the design of the study and is, together with JK responsible for the local conduct of the study at UMCG. GR contributed to the design of the study and is, together with PL responsible for the local conduct of the study at ETZ. AK contributed to the design of the study and is, together with GR responsible for the local conduct of the study at HMC. GH contributed to the design of the study and is, together with JK responsible for the local conduct of the study at UZG. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study received approval by the Medical Ethics Committee (METC Zuid-West Holland) This trial has been registered in the Dutch Trial Register (NTR) and is conducted in complicance with the European Union Clinical Trials Directive (2001/20/EC) and the principles of the Declaration of Helsinki (2013).

Consent for publication

By giving written informed consent, patients agree with the storage of data and publication of the study results.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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