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Resection versus biopsy in patients with glioblastoma (RESBIOP study): study protocol for an international multicentre prospective cohort study (ENCRAM 2202)

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ABSTRACT

Introduction There are no guidelines or prospective studies defining the optimal surgical treatment for glioblastomas in older patients (≥70 years), for those with a limited functioning performance at presentation (Karnofsky Performance Scale ≤70) or for those with tumours in certain locations (midline, multifocal). Therefore, the decision between resection and biopsy is varied, among neurosurgeons internationally and at times even within an institution. This study aims to compare the effects of maximal tumour resection versus tissue biopsy on survival, functional, neurological and quality of life outcomes in these patient subgroups. Furthermore, it evaluates which modality would maximise the potential to undergo adjuvant treatment.

Methods and analysis This study is an international, multicentre, prospective, two-arm cohort study of an observational nature. Consecutive patients with glioblastoma will be treated with resection or biopsy and matched with a 1:1 ratio. Primary endpoints are (1) overall survival and (2) proportion of patients that have received adjuvant treatment with chemotherapy and radiotherapy. Secondary endpoints are (1) proportion of patients with National Institute of Health Stroke Scale deterioration at 6 weeks, 3 months and 6 months after surgery; (2) progression-free survival (PFS); (3) quality of life at 6 weeks, 3 months and 6 months after surgery and (4) frequency and severity of serious adverse events. The total duration of the study is 5 years. Patient inclusion is 4 years; follow-up is 1 year.

Ethics and dissemination The study has been approved by the Medical Ethics Committee (METC Zuid-West Holland/Erasmus Medical Center; MEC-2020-0812). The results will be published in peer-reviewed academic journals and disseminated to patient organisations and media.

Trial registration number NCT06146725.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Resection is directly compared with biopsy in specific subgroups of patients with glioblastoma.
⇒ Predefined subgroup analyses for age, preoperative functional status and tumour location.
⇒ Propensity score matching to counteract expected confounding bias.

INTRODUCTION

Glioblastoma is the most common tumour which despite intensive treatment has a median survival of only 12–15 months.[1–3] Current standard treatment consists of surgery to establish diagnosis followed by a combination of adjuvant chemotherapy and radiotherapy.[2] While most surgeons advocate for maximal safe resection, there exists controversy over resection versus biopsy for older patients (≥70 years), those with a suboptimal functioning performance at presentation (Karnofsky Performance Scale (KPS) ≤70) and those with tumours in certain locations (midline). Therefore, surgical management differs considerably between caregivers and institutes.[4–6] Patients that are younger (<70 years) often undergo tumour resection since for these patients potential survival gain is of utmost priority. Older patients (≥70 years) are often approached more conservatively and a biopsy is preferred since some argue that in this subgroup preventing neurological deficits and maintaining quality of life (QoL) should be prioritised over potential survival gain.[7–12] For patients who are in suboptimal functioning performance at presentation (KPS≤70), the current evidence is even less clear.[13 14] When a diminished KPS is caused by neurological deficits, which in turn is caused by tumour mass effect or brain oedema, resection can be a solid option to improve neurological functioning, consequently improving the patient's QoL. In contrast, frail, older and those with significant comorbidities or cognitive impairments may not benefit from resection; as such, biopsy might be a better option

to confirm the diagnosis while maintaining function in order for the patient to be eligible to undergo adjuvant treatment. Previous studies have found that maximum tumour resection especially gross-total resection (GTR) is important to prolong survival and optimise the effect of the adjuvant treatment.[15–22] Evidence is accumulating that this might also be the case for patients ≥70 years or with KPS of ≤70.[15 23] Intuitively, resection and especially GTR might carry a higher risk of inducing neurological deficits than biopsy and therefore has the potential of impairing the QoL of a patient with already a dim life prognosis.[24 25] However, our own group has demonstrated that GTR in patients ≥70 years or with a KPS of ≤70 is associated with improved overall survival (OS) without a higher incidence of postoperative deficits.[15] The choice for either resection or biopsy in these patients is therefore highly based on personalised treatment, with the added incorporation of the location of the tumour, proximity to functional tissue or subcortical tracts, and the wishes of the patient and the family. We propose an international, multicentre, prospective cohort study to compare resection directly to biopsy in these patients. The primary study's objectives are to evaluate (1) if resection or biopsy yields superior outcomes in patients ≥70 years, with a KPS of ≤70, or with a midline or multifocal tumour, and (2) which patients benefit the most from resection or biopsy, for which outcomes, and how they could be identified preoperatively. The results from this study will aid neurosurgeons in the surgical decision-making process and consequently optimise treatment outcomes. The study will be carried out by the centres affiliated with the European and North American Consortium and Registry for Intraoperative Mapping (ENCRAM).[26]

METHODS/DESIGN

Trial design

This is an international, multicentre, prospective, observational, two-arm cohort study (registration: clinicaltrials.gov ID number NCT06146725). Eligible patients are treated with either resection or biopsy and matched with a 1:1 ratio with a sequential computer-generated random number as subject ID. The study is planned to be active between 2023 and 2029.

Study objectives

The primary study objective is to evaluate the safety and efficacy of resection versus biopsy in glioblastoma patients as measured by OS and receipt of adjuvant treatment with chemotherapy and radiotherapy. Secondary study objectives are to evaluate postoperative neurological morbidity, progression-free survival (PFS), postoperative QoL and SAEs after resection or biopsy as measured by National Institute of Health Stroke Scale (NIHSS) deterioration, tumour progression on MRI scans, quality of life questionnaires (QLQ-C30, European Organisation for Research and Treatment of Cancer (EORTC) QLQ-BN20, EQ-5D) and recording SAEs, respectively.

Study setting and participants

Patients will be recruited from the neurosurgical or neurological outpatient clinic or through referral from general hospitals of the participating neurosurgical hospitals, located in Europe and the USA. The study is carried out by centres from the ENCRAM Consortium.

Patient and public involvement statement

Patients enrolled in the SAFE trial (awake craniotomy vs craniotomy under general anaesthesia for patients with glioblastoma, NCT03861299) were consulted for this study to include patient experiences with the shared decision-making process regarding the surgical treatment options.

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. Suspected glioblastoma on MRI as assessed by the neurosurgeon
3. Written informed consent

Exclusion criteria

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

1. Tumours of the cerebellum or brainstem.
2. Medical reasons precluding MRI (eg, pacemaker).
3. Inability to give written informed consent.
4. Secondary high-grade glioma due to malignant transformation from low-grade glioma
5. 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.

Interventions

Resection under general anaesthesia

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, the patient is orotracheally intubated and mechanical ventilation is applied. Respiratory rate and tidal volume are adjusted to keep the patient normocapnic. Patients typically receive 1–2 g of cefazolin and sometimes up to 1 g/kg of mannitol (all verified with the surgeon). An arterial line (with standard monitoring for vital signs in addition to BP monitoring), central venous catheter and urinary 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 (a beta blocker or calcium channel blocker may be used to control BP as an alternative to clonidine). The fluid management is aiming for normovolaemia. 0.9% saline solution and balanced crystalloids are used for maintenance; in case of blood loss >300 mL, HAES 130/0.4 (hydroxyethyl starch) 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 hyperglycaemia will be treated with insulin, if necessary. The anaesthetised patient is positioned on the table. Local infiltration of the scalp is performed with 20 mL lidocaine 1% with epinephrine 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 neuropsychological monitoring, guided by standard neuronavigation. Tumour resection continues until maximum safe resection has been achieved as per the neurosurgeon's opinion. At the end of the procedure, all anaesthetics are stopped and the patient is brought to the post-anaesthesia care unit (PACU). Detubation of the patient is performed as early as possible, if the 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 intravenously or orally 1 g up to 4 dd and morphine 7.5 mg subcutaneously up to 4 dd, if necessary. At the PACU, the patient is hemodynamically and neurologically monitored for 24 hours.

Biopsy under general anaesthesia

The biopsy procedure is identical to the procedure as described above, but no arterial lines are placed in patients who will undergo a biopsy. A biopsy of the tumour is guided by neuronavigation. Patients who receive biopsy do not stay overnight at the PACU but are monitored in the neurosurgical ward.

Surgical adjuncts and additional imaging

The use of intraoperative mapping techniques, fMRI, diffusion tensor imaging (DTI), ultrasound or 5-aminolevulinic acid is allowed to be used on the surgeon's indication.

Participant timeline

The flow diagram illustrates the main study procedures, including follow-up evaluations (figure 1). In summary, study patients are allocated to either the supramaximal or the maximum safe resection group and will undergo evaluation at presentation (baseline) and during the follow-up period at 6 weeks, 3 months and 6 months postoperatively. The motor function will be evaluated using the NIHSS . Cognitive function will be assessed using the Montreal Cognitive Assessment (MOCA). Patient functioning will be assessed with the KPS and the American Society of Anesthesiologists (ASA) physical status classification system. Health-related quality of life (HRQoL) will be assessed with the EORTC QLQ-C30, EORTC QLQ-BN20 and EQ-5D questionnaires. We expect to complete patient inclusion in 4 years. The estimated duration of the study (including follow-up) will be 5 years.

Study procedures: clinical evaluations and follow-up

- Pre-operative (baseline) CRF (case report file)
  - Unique subject ID, demographics (centre, country, year, gender, age), preoperative tumour volume, hemisphere, lobe, multifocality, functional areas, use of steroids (if yes, specify if there was neurological improvement), preoperative KPS, ASA score, preoperative neurological status (NIHSS), MRC (Medical Research Council) scale arm and leg, neurolinguistic testing, MOCA, QoL questionnaires (QLQ-C30, QLQ-BN20, EQ-5D).
- Surgery CRF
  - Modality, intraoperative mapping performed (if yes, specify modality), use of surgical adjuncts (if

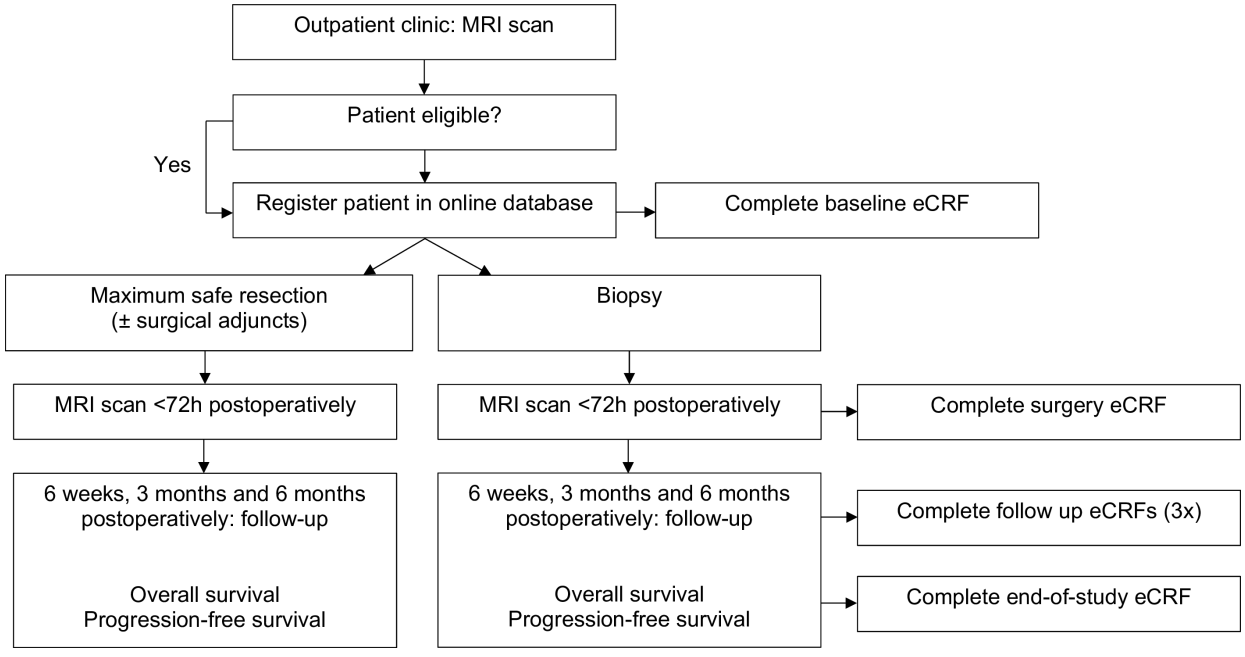

Figure 1 Study flowchart.

DTI, integrity of tracts), use of additional imaging, goal of surgery, rationale for treatment, radiological factors (resection percentage and residual volume of CE and NCE tumour, postoperative ischaemia, postoperative bleeding).

- Follow-up CRFs
  - 6 weeks postoperatively (±1 week): histology and molecular markers (WHO grade, MGMT status, IDH-1 status, CDKN2A/B status), neurological status (NIHSS), KPS, MOCA, QoL questionnaires (QLQ-C30, QLQ-BN20, EQ-5D), serious adverse events (SAEs).
  - 3 months postoperatively (±2 weeks): neurological status (NIHSS), KPS, neurolinguistic testing, MOCA, QoL questionnaires (QLQ-C30, QLQ-BN20, EQ-5D).
  - 6 months postoperatively (±2 weeks): neurological status (NIHSS), KPS, MOCA, QoL questionnaires (QLQ-C30, QLQ-BN20, EQ-5D), standard adjuvant treatment with chemotherapy and radiotherapy started and/or completed, number of temozolomide cycles, number of radiotherapy fractions given, total dose radiotherapy in Gy, other adjuvant treatment
- Survival CRF
  - OS, PFS (clinical, radiological, both)

Outcomes

Primary outcome measures

The primary outcomes are (1) OS defined as the time from diagnosis to death from any cause and (2) the proportion of patients who have received adjuvant treatment with chemotherapy and radiotherapy.

Secondary outcome measures

The secondary outcomes are (1) proportion of patients with NIHSS deterioration at 6 weeks, 3 months and 6 months after surgery; (2) PFS as time from diagnosis to disease progression (occurrence of a new tumour lesion with a volume greater than 0.175 cm^3 or an increase in residual tumour volume of more than 25%) or death, whichever comes first; (3) QoL as assessed by the EORTC QLQ-C30, EORTC QLQ-BN20 and EQ-5D questionnaires at 6 weeks, 3 months and 6 months after surgery; and (4) frequency and severity of SAEs in each arm.

National Institutes of Health Stroke Scale

The NIHSS is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke but has been used extensively for outcomes in glioma surgery because of the lack of such a scale for neuro-oncologic purposes and has been validated. The NIHSS is composed of 11 items, each of which scores a specific ability between 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, and the minimum score 0.

Montreal Cognitive Assessment

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, and the cut-off score is ≤26.

EuroQol-5D

The EQ-5D is a standardised questionnaire to assess the general HRQoL in five domains: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. It was developed by the EuroQol Group and can also be used to calculate quality-adjusted life years for cost-utility analyses.

QLQ-C30 and QLQ-BN20

The QLQ-C30 and QLQ-BN20 are standardised questionnaires that have been designed by the EORTC. They are used to assess the QoL in patients with cancer in general (C30) and patients with brain tumour (BN20) by incorporating functional scales (physical, role, cognitive, emotional, social) and symptom scales (fatigue, pain, nausea and vomiting, seizures, communicating).

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 Bonferroni correction for multiple testing. The sample size calculations that follow take that into account. For the first primary endpoint, OS, we assume a median survival time of 9 months in the control group (biopsy), and 12 months in the experimental group (resection). A two-sample test for proportions with continuity correction requires 512 patients (256 per arm) in total in order to detect the above-mentioned difference of 10% with 95% power at a 1% significance level. For the second primary endpoint, the proportion of patients with adjuvant treatment with chemotherapy and radiotherapy, we assume a proportion of 50% in the control group (biopsy) and 60% in the experimental group (resection). A two-sample test for proportions with continuity correction requires 290 patients (145 per arm) in total in order to detect the above-mentioned difference of 10% with 95% 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, that is, 512. A total of 750 eligible and evaluable patients in two arms allow the difference of 10% in the proportion of patients with adjuvant treatment with chemotherapy and radiotherapy to be detected with 99% power. Taking into account possible ineligibility and withdrawal of consent (we estimate this at 10%), a total of 564 patients should be included (282 patients per arm). Since propensity score matching with a 1:1 ratio will be performed, 564 patients will be included after matching: 282 patients in the resection arm and 282 patients in the biopsy arm. Since we estimate that (1) the distribution of patients

aged <70 vs ≥70 is 1:1, (2) the distribution of patients with a preoperative KPS of ≤70 vs >70 is 1:2 and (3) the distribution of patients with a lobar or unifocal tumour versus midline or multifocal tumour is 3:1, we will include a total of 1692 patients: 846 patients in the resection arm and 846 patients in the biopsy arm after matching.

Data collection

All patient data is collected in the electronic data software Castor EDC. This software allows built-in logical checks and validations to promote data quality. Data entry and group allocation are performed by the study coordinator or locally by trained physicians and research nurses under supervision of the local investigator.

Data analysis

All analyses will be according to the intention to treat principle, restricted to eligible patients. Patients initially registered but considered ineligible afterwards based on the histological analysis of tissue extracted during surgery will be excluded from all analyses.

Primary study parameters

OS will be analysed using the Kaplan-Meier method to estimate OS proportions per treatment group at appropriate time points, while the Greenwood estimate of the SE will be used to construct the corresponding 95% CI. Multivariate Cox proportional hazards models will be built for OS where treatment group effect will be corrected for the minimisation factors age, preoperative KPS, preoperative NIHSS, preoperative ASA, histopathological grading, molecular status, intraoperative mapping and surgical adjuncts, and tumour location. The receipt of adjuvant Stupp treatment will be analysed using the χ^2 test, supplemented by multivariate logistic regressions to evaluate predictors. Subgroup analyses for tumour grade (WHO grade III/IV), molecular status, preoperative NIHSS, preoperative KPS, age, intraoperative mapping and tumour location will be performed.

Secondary study parameters

The Kaplan-Meier method will be used to estimate PFS proportions per treatment group at appropriate time points, while the Greenwood estimate of the SE will be used to construct the corresponding 95% CI. Multivariate Cox proportional hazards models will be built for OS where treatment group effects will be corrected for the minimisation factors age, preoperative KPS, preoperative NIHSS, preoperative ASA, histopathological grading, molecular status, intraoperative mapping and surgical adjuncts, and tumour location. The proportion of patients with NIHSS deterioration and/or QoL deterioration will be analysed using the χ^2 test, supplemented by multivariate logistic regressions to evaluate predictors. SAEs in both groups will be described.

Study monitoring

No scheduled on-site monitoring visits will be performed. Local investigators will remain responsible for the fact 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 good clinical practice and with the applicable regulatory requirement(s). Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. No Data Safety Monitoring Board will be installed; all interventions are care-as-usual and patients are allocated without randomisation.

AEs and SAEs

Adverse events (AEs) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to neurosurgery. All AEs reported spontaneously by the subject or observed by the investigator or his staff will be recorded from the start of surgery until 6 weeks after surgery. SAEs are any untoward medical occurrence or effect that results in death; is life-threatening (at the time of the event); requires hospitalisation or prolongation of existing inpatients' hospitalisation; 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 on appropriate judgement by the investigator. An elective hospital admission will not be considered as an SAE. Most of the (serious) adverse effects of treatments are mainly related to the surgery: postoperative pain, nausea and anaemia (in case of massive blood loss), infections, intracranial haemorrhage, epilepsy, aphasia, paresis/paralysis in arms or/and legs.

Most of the (serious) adverse effects of treatments will be mainly related to the surgery: postoperative 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 is a well-known risk/complication of the craniotomy and can be attributed to the nature of the operation. Neurosurgical clinics are well adapted to prevent and treat such events. SAEs will be collected through routine data management.

Publication of results

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

Ethics and dissemination

The study has been approved by the Medical Ethics Committee (METC Zuid-West Holland/Erasmus Medical Center; MEC-2020-0812) and is conducted in compliance with the European Union Clinical Trials Directive (2001/20/EC) and the principles of the Declaration of Helsinki (2013). The results of the study will be published

in peer-reviewed academic journals and disseminated to patient organisations and media.

DISCUSSION

Maximal safe resection of contrast-enhancing tissue has demonstrated benefit for patients; however, there is a debate for those older (≥70 years), with a limited functioning performance at presentation (KPS≤70) or with a certain tumour location (midline, multifocal).[15–23] Some argue that limited survival gains for increased surgical risk of postoperative neurological morbidity and impaired QoL can be justified. As a result, the surgical treatment of patients with glioblastoma shows major differences between countries, hospitals and surgeons.[4–6] The heterogeneity in this decision-making becomes evident in the Dutch QRNS data, which showed that some centres perform in up to 60% of older patients with glioblastoma a biopsy compared with only 20% in others.[6] A possible difference in caseload or patient characteristics could be argued, though this is highly unlikely since there exists a multi-centralised referral system for brain tumours in the Netherlands which leads to a relatively evenly spread distribution of patients and subgroups throughout the Netherlands.[6] Furthermore, this heterogeneity has been confirmed in a global survey[4] and therefore, seems to be an undesirable effect of the lack of robust scientific evidence on this subject and a result of subjective local differences. The lack of evidence regarding the optimum treatment for these patients is in our opinion twofold. First, there is a lack of prospective evidence regarding survival benefits for patients of ≥70 years or with a KPS of ≤70 undergoing a resection versus biopsy. The only prospective randomised controlled trial on this subject was published in 2003.[27] This small Finnish study of 23 patients with glioblastoma showed a significant prolonging of survival in patients who received a resection for their tumour compared with patients who underwent a biopsy only. However, the study size was not adequately powered—because no sample size calculation had been made before the onset of the study, resulting in a small study size—and the resection group and the biopsy group significantly differed on a number of preoperatively strong prognostic characteristics like age and KPS. The study's conclusions are therefore fairly unreliable. Second, very few studies have assessed QoL as a postoperative outcome measure in patients with glioblastoma.[28–31] These outcome measures might be equally or even more important for this category of patients than the actual survival period due to their dim prognosis and play a major role in this subgroup's surgical decision-making process. The lack of prospective evidence with adequate depth and breadth currently hampers the neurosurgeon's possibility of making an evidence-based decision about the optimum treatment for these patients. We therefore propose an international, multicentre, prospective study to evaluate if maximum safe resection is an effective and feasible surgical choice for patients with glioblastoma ≥70 years, with a KPS of ≤70, or with a midline or multifocal tumour. Furthermore, the study will aim to determine which individual patients would benefit the most from resection or biopsy, for which outcomes and how they could be identified preoperatively. This initiative is the first to directly compare resection versus biopsy in their ability to improve patient outcomes for survival, QoL, receipt of adjuvant therapy and neurological morbidity.

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Contributors JKWG designed the study, wrote the study protocol and is end-responsible for the implementation and organisation of the study in all participating centers as well as the conduct of the database. SMK and CJ contributed to the design of the study and are responsible for the local conduct of the study in Heidelberg. SI contributed to the design of the study and is responsible for the local conduct of the study in Munich. PS contributed to the design of the study and is responsible for the local conduct of the study in Bern. BVN contributed to the design of the study and is responsible for the local conduct of the study in Boston. MLDB contributed to the design of the study and is responsible for the local conduct of the study in The Hague. MB and JSY contributed to the design of the study and are responsible for the local conduct of the study in San Francisco. SDV contributed to the design of the study and is responsible for the local conduct of the study in Leuven. AJPEV contributed to the design of the study and is responsible for the local conduct of the study in Rotterdam. All authors read and approved the final version of the manuscript. JKWG and AJPEV are responsible for the overall content as guarantors.

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