The SAFE-trial: Safe Surgery for Glioblastoma Multiforme: Awake Craniotomy versus Surgery under General Anesthesia. A multicenter prospective randomised controlled study

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The study will take place in 5 neurosurgical centers in the Netherlands (Erasmus MC, UMC Utrecht, Elizabeth Ziekenhuis Tilburg, MC Haaglanden The Hague, UMCG Groningen) and one center in Belgium (UZ Gent). All centers have ample experience with the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON48603

Source
ToetsingOnline

Brief title
The SAFE-trial

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Nervous system neoplasms malignant and unspecified NEC
- Nervous system, skull and spine therapeutic procedures

Synonym
Brain malignancy, brain tumor

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: KWF

Intervention

Keyword: Awake craniotomy, Glioblastoma, Gross Total Resection, Quality of life

Outcome measures

Primary outcome

1. To investigate if the percentage of neurologic morbidity 6 weeks after surgery in patients with GBM in eloquent areas, operated with an awake craniotomy (AC) is significantly lower as compared to patients operated under general anesthesia (GA).

2. To investigate if the percentage of patients with a total resection with GBM in eloquent areas, operated with an awake craniotomy (AC) is significantly higher as compared to patients operated under general anesthesia (GA). The amount of total resections is measurable and has a direct relationship with the prognosis of the patients with GM.

Secondary outcome

1.To assess quality of life in patients with GM in eloquent areas operated with an awake craniotomy (AC) as compared to patients operated under general anesthesia (GA) at 6 weeks, 3 months and 1 year after operation.

2. To assess if median survival, progression free survival and overall survival

after 1 year in patients with GM in eloquent areas operated with an awake craniotomy (AC) procedure is significantly higher as compared to patients operated under general anesthesia.

Study description

Background summary

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. The annual incidence is approximately 5 per 100.000 with a prevalence of 800-1000 cases each year in the Netherlands. Patients usually present with speech difficulties, unilateral paresis in arms and/or legs, headache, cognitive problems or epilepsy. Multiple studies show that extent of resection of the tumor improves survival in patients with GM. 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. Thus, in addition to the survival benefit associated with maximum cytoreductive surgery such surgery seems essential for the efficacy of modern adjuvant treatment.
More than 50% of GM's 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 locate. 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 GMs 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. However, partial or subtotal resections will benefit less from radio and chemotherapy as total resections. 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.

Study objective

The study will take place in 5 neurosurgical centers in the Netherlands (Erasmus MC, UMC Utrecht, Elizabeth Ziekenhuis Tilburg, MC Haaglanden The Hague, UMCG Groningen) and one center in Belgium (UZ Gent). All centers have ample experience with the AC technique. When patients with a GBM fulfill the inclusion criteria on MRI, they will be informed by a neurosurgeon regarding participating in the trial. The randomisation will take place in Rotterdam by

the controlled trial center (CTC). After informed consent, the patient will be informed about the procedure. Preoperatively, a full neurological exam will be carried out as well as two questionnaires regarding quality of life and a neurolinguistic test-battery. Standard preparation before the operation, the operation itself (awake or general anaesthesia) and postoperative care will take place in the referenced hospitals. A MRI scan 48 hours before- and after the operation will be done. The patient will then be treated with radiotherapy and chemotherapy. At 6 weeks, 3 months and 6 months after the operation, a full neurological exam will be carried out again as well as two questionnaires. After 3 months, the neurolinguistic test-battery will be carried out again. The survival of the patients will be documented. After all the data have been collected, the statistical analyses will take place. With this analysis, significant differences between the groups for the primary and secondary outcomes measures will be calculated.

Study design

The trial is set up as a multicenter randomized controlled study. Patients with glioblastomas in eloquent areas on diagnostic MRI will be selected by the neurosurgeons according the eligibility criteria. After written informed consent the patient will be randomized for awake craniotomy (AC) or regular craniotomy under general anesthesia (GA). After surgery, only patients with histologically proven GBM will be included in the study. Thereafter, patients will receive the standard treatment with concomitant temozolamide and radiation therapy and standard follow up. Primary outcome is neurological morbidity on the NIHSS scale at 6 weeks after surgery and percentage of patients with total resection on post operative MRI. Secondary outcome is HRQoL at 6 weeks, 3 months and 6 months after surgery, progression free survival at 6 months and overall survival after 2 years. Total duration of the study is 4 years. Patient inclusion is 3,5 years. Follow-up is 1 year. Statistical analysis, cost benefit analysis and article writing will taken 6 months.

Intervention

An awake craniotomy

Study burden and risks

Assessments:
- Neurological examination: 15 minutes. Will take part 4 times. Before the operation, and 6 weeks, 3 months and 6 months after the operation.
- Questionnaires: 10 minutes. Will take part 4 times. Before the operation, and 6 weeks, 3 months and 6 months after the operation.
- Neurolinguistic test-battery: 30 minutes. Will take part 2 times. Before the operation and 3 months after the operation.
- MRI-scan: before the operation, 48 hours after the operation, and then after

3 months and 6 months. These MRI are part of the standard/usual care.

Possible complications:
- bleeding
- infection
- paresis/paralysis of extremities
- speech problems
- epilepsy
- death

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age >18 years

2. Tumor diagnosed as Glioblastoma Multiforme on MRI with 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, sensor cortex, subcortical pyramidal tract or speech areas as indicated on MRI (Sawaya Grading II and II)
4. The tumor is suitable for resection (according neurosurgeon)
5. Karnofsky performance scale 80 or more
6. No severe aphasia or dysphasia; able to communicate during an awake procedure
7. Written Informed consent

Exclusion criteria

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 (eg, pacemaker)
5. Inability to give consent because of a 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

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2019
Enrollment:	220
Type:	Anticipated

Ethics review

Approved WMO Date:	16-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03861299
CCMO	NL66673.078.18