RESURGE - Randomized Controlled Comparative Phase II Trial on Surgery for Glioblastoma Recurrence

Published: 10-10-2019
Last updated: 12-04-2024

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

Summary

ID

NL-OMON50585

Source
ToetsingOnline

Brief title
RESURGE

Condition

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

Synonym
primary brain tumor; glioma

Research involving
Human

Sponsors and support

Primary sponsor: Universitätsklinik für Neurochirurgie, Inselspital
Source(s) of monetary or material Support: Ministerie van OC&W,Bernische Krebsliga

Intervention

Keyword: glioblastoma, neurosurgery, recurrence

Outcome measures

Primary outcome

The primary outcome is overall survival (OS) in all patients and in subgroups stratified by extent of resection.

Secondary outcome

Secondary outcomes are:

Recruitment rate for all screened patients. The recruitment rate analysis will be used to adapt the number of participating centers.

Overall survival (OS) estimates are treatment hazard ratio (OS HR), median overall survival (mOS), overall survival probability at 6 months (OS6) and overall survival probability at 12 months (OS12).

Progression-free survival (PFS) estimates are treatment hazard ratio (PFS HR), median progression-free survival (mPFS) and progression-free survival probability at 6 months (PFS6).

Cross-over rate

Morbidity of surgery rate Neurological deterioration

The EORTC Quality of Life C30 and BN20 questionnaires (QLQ), Mini Mental Status Examination (MMSE) and Karnofsky Performance Score (KPS) will be used to assess the quality of life.

Total number of days spent at home is assessed after the patient`s death, and is used as a surrogate parameter for days with good quality of life.

Total number of days spent outside home at hospital, rehabilitation or nursing

facility.

The above mentioned outcomes were selected to ensure comparability with other

trials and to

determine the safety of the procedure.

Study description

Background summary

Background
Glioblastoma is a malignant, locally invasive brain tumor whose prognosis remains grim despite various intense treatment modalities (Tait et al., 2007). In the past, radical surgery was met with skepticism due to the aggressive infiltrative character of the tumor. However, an increasing number of retrospective studies over the last decade suggest a survival benefit for surgery (Lacroix et al., 2001; Sanai et al., 2011). A recent post-hoc analysis of a randomized controlled trial on the use of the surgical adjunct 5-ALA reported a prolonged overall survival from 11.9 to 16.7 months (evidence level 2a; Stummer et al., 2006; Stummer et al., 2008) after more extensive resection. Thus, maximal safe resection has become a mainstay of treatment for newly diagnosed glioblastoma (Mason et al., 2007), followed by adjuvant radio-chemotherapy (Stupp et al., 2005; Weller, 2011).
Glioblastoma almost invariably recurs after a median of 6.9 months (Stupp et al., 2005), leaving but few options for further treatment (Stupp et al., 2009). Recurrence of glioblastoma after surgery and concomitant adjuvant therapy represents an additional therapeutic challenge and may be treated with second-line pharmacotherapy. In addition, a second surgery may also be considered in highly selected patients (Mason et al., 2007).
Rationale
The rationale for surgery - maximum safe resection - is to prolong survival through reduction of tumor load, and, maybe due to an increased efficacy of adjuvant treatment (Stummer et al., 2011). However, surgery carries risks of complications, that may result in a decreased functional and survival outcome (Hoover et al., 2013). The crucial question therefore is whether, to what extent, and at what costs in terms of neurological risks a second resection prolongs survival.
The purpose of the study is to compare the effect of craniotomy and tumor resection followed by adjuvant second-line therapy to no surgery followed by second-line therapy on overall survival, neurological status, and quality of life. Analysis of overall survival will be used to improve sample size estimation of a subsequent phase III trial for craniotomy and tumor resection

of glioblastoma recurrence in cooperation with the EORTC.

Study objective

Overall Objective
The purpose of the study is to compare the effect of craniotomy and tumor resection followed by adjuvant second-line therapy to no surgery followed by second-line therapy on overall survival, neurological status, and quality of life. Analysis of overall survival will be used to improve sample size estimation of a subsequent phase III trial for craniotomy and tumor resection of glioblastoma recurrence in cooperation with the EORTC.

Primary Objective
The primary objective of this randomized trial is to compare patient survival after surgery followed by adjuvant second-line therapy to no surgery followed by second-line therapy in recurrent glioblastoma. An auxiliary objective to primary objective is to compare the survival of operated patients to control in the subgroups stratified by extent of resection .

Secondary Objectives
Secondary objectives are:
Assessment of recruitment for all screened patients, comparison of progression-free survival between treatment arms, evaluation of crossover and comparison of patient quality of life between treatment arms.

Safety Objectives
Safety objectives are to assess neurological deficits, local infections and morbidity associated to surgery and hospital stay after surgery and during follow-up. Total time spent at home, and total time spent outside home at hospital, rehabilitation or nursing facility will be assessed and compared between both study arms.

Study design

This is a randomized (2:1), parallel-group, controlled, non-blinded, comparative phase II trial in patients with recurrent glioblastoma. The aim of the study is to assess the effect of craniotomy and tumor resection followed by adjuvant second-line therapy versus second-line therapy alone on overall survival, progression-free survival, neurological status and quality of life. These results may serve as the basis of a subsequent randomized controlled phase III trial for craniotomy and tumor resection of glioblastoma recurrence in cooperation with the EORTC.
All patients presenting at the participating centres with radiological suspicion of first glioblastoma recurrence will be screened according to the inclusion criteria. After completed local screening and prior to patient recruitment the encoded preoperative MRI will be sent by e-mail to the study

eligibility committee which consists of two members of the steering committee (Prof. Andreas Raabe, Bern and Prof. Luca Regli, Zurich). They will assess the resectability of the recurrence based on the preoperative MRI within 24h and they may overrule the local investigator. Study participation will be proposed to the patient by one of the investigators. Reasons for non-participation for randomization will be noted for recruitment analysis. Patients participating in the clinical trial are randomized for surgery followed by adjuvant second-line therapy (interventional group) or second-line therapy alone (control group) in a 2:1 ratio. A design with a 2:1 ratio was chosen because patients of the interventional group are likely to differ in terms of the surgical results: Based on our own data and the literature (Quick et al., 2014) we assume a 50% complete resection of enhancing tumor (CRET) rate, leaving the other 50% with an incomplete resection. According to the literature the extent of resection is an important predictive factor for overall survival (for initial glioblastoma: Stummer et al., 2008; for recurrent glioblastoma: Quick et al., 2014). The trial design with the 2:1 ratio takes the surgical result into account and permits a comparison between cohorts of complete and incomplete resection of the interventional group and the control group. Treatment allocation is balanced for MGMT promoter status and study site at initial diagnosis (stratification).
Eligible patients who are not willing to be randomized or to participate in the randomized trial will be asked to give their consent for the participation in an additional observational arm. In this arm details of treatment, progression-free survival, overall survival, neurological outcomes and number of days spent at home/outside home will be assessed, independent of treatment.
Patients allocated to the interventional group are to be operated within 14 days from inclusion and within 21 days from the MRI on which recurrence was diagnosed and referred to the treating neurooncologist after discharge for adjuvant second-line therapy as soon as the patient`s condition after surgery permits. Patients allocated to the control group are to be seen by the treating neurooncologist following study inclusion and second-line therapy is to be started within 14 days after study inclusion. Type of (adjuvant) second-line therapy is determined by the treating neurooncologist according to local and general guidelines and is not specified by the study protocol. Follow-up visits consist of a cerebral MRI scan, medical history and physical examination. Follow-up visits are scheduled every 3 months after study inclusion for up to 24 months (minimal follow-up is 12 months for last patient in) or death.

Intervention

Surgery must take place between day 1 and 14 after study inclusion and within 21 days from the MRI on which recurrence was diagnosed. The modalities of surgery and the choice of pre- and intra- operative technical adjuncts is at the treating neurosurgery discretion and recorded in the electronic case report forms (eCRFs). However, some form of intra-operative resection control (iMRI or intra- operative fluorescence) and function control (electrophysiology) should be available to the surgeon and used when warranted. Patients will be seen

after surgery by the treating neurooncologist to discuss modalities of adjuvant second-line therapy. Type of adjuvant second-line therapy is not stipulated by the study protocol. Modalities of pharmacotherapy, administered doses, duration of treatment, adverse events and further therapies are reported on the eCRFs by the neurooncologist.

Study burden and risks

Benefits of surgery for recurrent glioblastoma
The aim of surgery at glioblastoma recurrence is to prolong survival through reduction of tumor load. Retrospective single center studies suggest comparatively long survival times after re-operation. A recent report observed a mean survival after re-operation of 13.5 months (Quick et al., 2014). Of note, patients who received a complete resection of enhancing tumor (CRET) at recurrence had a longer survival than those who received an incomplete resection (15.3 months versus 8.6 months, respectively). The yet largest retrospective report stratified all glioblastoma patients who underwent tumor resection according to the number of resections received and found mean overall survival times of 6.8, 15.5 and 22.4 months for 1, 2 and 3 resections, respectively ($p<0.05$, 578 patients, Chaichana et al., 2013). A multicenter, retrospective investigation on >500 patients reports a mean overall survival of >25 months in patients with repeat surgery (Ringel et al., unpublished results). These relatively long survival times appear favorable compared to patients who did not receive surgery at recurrence (Stupp et al., 2005). However, these data are non-controlled.
A meta-analysis of 300 patients in eight EORTC randomized controlled trials on second-line pharmacotherapy showed identical survival rates for patients with and without surgery at recurrence (median survival 7.1 months after recurrence for both subgroups, Figure 1). However, only a minority of patients (n=20) underwent resection and the extent of resection is unknown (Gorlia et al., 2012).
Risks of surgery for recurrent glioblastoma
Wound healing difficulties, cerebrospinal fluid leaks, hydrocephalus requiring ventriculo-peritoneal shunt implantation, infections, edema and neurological deficits have all been described as morbidity of initial and repeated surgery (Samis Zella et al., 2014). Surgically acquired major permanent neurological deficits have become an unlikely event at the first resection (3.8%, Schucht et al., 2012). Whether a surgery for recurrent glioblastoma represents a higher risk of permanent neurological deficit is unclear. A recent report found identical rates of 13% for new motor and speech deficits following primary and repeated surgery (Chaichana et al., 2013). Gempt et al. (2013) observed a higher rate of neurological deficits of 16% (2/25) after recurrent surgery compared to 7% (6/84) after initial surgery, presumably due to a higher rate of postoperative ischemic changes (80% vs 31% for recurrent vs. initial surgery, $p<0.01$). Similarly, Hoover et al. (2013) found a higher incidence of neurological deficits in patients after repeated surgery (12.1% vs. 4.8% at first surgery) and a higher risk for overall complications (including

neurological deficits, wound problems and systemic complications) of 27.0% after repeated surgery compared to 12.8% after first surgery (p=0.0068). Dutzmann et al. (2012) also compared complications of initial and repeat surgeries, and found the risk for new neurological deficits to be similar (10.0% and 10.6% for initial and repeat surgeries, respectively). The same group recently published a retrospective analysis on 40 patients with recurrent glioblastoma deemed eligible for a gross total resection (Quick et al., 2014). 12.5% showed a new or worsening of an already existing neurological deficit, 5% suffered from postoperative cerebrospinal fluid fistula leading to wound revision, and 2.4% had a wound infection. Chang et al. (2003) observed a higher rate of 18% worsened neurological status after repeat surgery compared to 8% after initial surgery in (91 and 408 patients, respectively; p = 0.007). Systemic infections (4.4%) were also more frequent after repeated than after initial surgery (0%, P<0.0001).
Risks of surgery may negatively impact its benefit for survival
Surgically acquired neurological deficits lead to decreased life expectancy in addition to the obvious loss of quality of life (McGirt et al., 2009). A single center report retrospectively stratified patients according to treatment at recurrence, and found mean survival duration after recurrence of 5, 6, 9 and 14 months for palliative treatment, surgery only, chemotherapy only and surgery plus chemotherapy, respectively (De Bonis et al., 2013). Surgery alone did not provide a survival benefit, which might at least partially be due to a high rate of patients who did not receive adjuvant second-line therapy after surgery due to major surgical morbidity (48%).

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

- age at least 18 years old
- good clinical condition
- the recurrent glioblastoma was operated and irradiated once

Exclusion criteria

- the last radiotherapy was completed at least three months before inclusion

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-11-2019
Enrollment:	30

Type:	Actual

Ethics review

Approved WMO Date:	10-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NCT02394626
CCMO	NL65118.029.18