Study Protocol: Early Stereotactic Gamma Knife Radiosurgery to Residual Tumor After Surgery of Newly Diagnosed Glioblastoma (Gamma-GBM)

**BACKGROUND:** Glioblastoma (GBM) is the most common malignant brain tumor in adult patients. Tumor recurrence commonly occurs around the resection cavity, especially after subtotal resection (STR). Consequently, the extent of resection correlates with overall survival (OS), suggesting that depletion of postoperative tumor remnants will improve outcome.

**OBJECTIVE:** To assess safety and efficacy of adding stereotactic radiosurgery (SRS) to the standard treatment of GBM in patients with postoperative residual tumor.

**METHODS:** Gamma-GBM is a single center, open-label, prospective, single arm, phase II study that includes patients with newly diagnosed GBM (intraoperative via frozen sections) who underwent STR (residual tumor will be identified by native and contrast enhanced T1-weighted magnetic resonance imaging scans). All patients will receive SRS with 15 Gy (prescribed to the 50% isodose enclosing all areas of residual tumor) early (within 24-72 h) after surgery. Thereafter, all patients undergo standard-of-care therapy for GBM (radiochemotherapy with 60 Gy external beam radiotherapy [EBRT] plus concomitant temozolomide and 6 cycles of adjuvant temozolomide chemotherapy). The primary outcome is median progression-free survival, secondary outcomes are median OS, occurrence of radiation induced acute (<3 wk), early delayed (<3 mo), and late (>3 mo post-SRS) neurotoxicity and incidence of symptomatic radionecrosis.

**EXPECTED OUTCOMES:** We expect to detect efficacy and safety signals by the immediate application of SRS to standard-of-care therapy in newly diagnosed GBM.

**DISCUSSION:** Early postoperative SRS to areas of residual tumor could bridge the therapeutic gap between surgery and adjuvant therapies.

**KEY WORDS:** Glioblastoma, Stereotactic radiosurgery, Surgery

**GENERAL INFORMATION**

**Protocol Title:** Early Stereotactic Gamma Knife Radiosurgery to Residual Tumor After Surgery of Newly Diagnosed Glioblastoma (Gamma-GBM)

**Protocol Identifying Number:** Clinicaltrials.gov identifying number: NCT03055208 (registration date February 16, 2017)

**Sponsor/Funding Agency:** This trial is sponsored by the University of Heidelberg/University Medical Center Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. Financial support was provided by ELEKTA Instrument AB, Kungstensgatan 18, 11 357 Stockholm, Sweden.

**Investigators:** Principle investigator of Gamma-GBM is F.W. Patients will be screened and included by S.B., F.A.G., M.S.R., and D.H. The study is led by F.W. per pro F.A.G. and S.M. F.S. is in charge of physical/treatment planning.
aspects. A.F. and C.G. contribute and review neuroradiological aspects. The results will be interpreted by S.B., M.G., A.F., and F.A.G.

RATIONALE AND BACKGROUND INFORMATION

Glioblastoma (GBM) is the most common malignant brain tumor in adult patients. Despite multimodal therapy consisting of surgery, radiotherapy, and chemotherapy, the median overall survival (OS) currently is 14 to 16 mo.\(^1\) It is well known that the extent of resection is a key factor for survival\(^2,3\) and that most recurrences develop at the edge of the surgical margin and especially around areas of residual tumor.\(^4-6\)

Physicians can identify residual tumor in early postoperative magnetic resonance imaging (MRI) scans (24-72 h after surgery),\(^7\) providing a window of opportunity to treat these regions. Although second-look surgery may be performed, most cases where residual tumor is visible in early postoperative scans did not allow more aggressive surgery due to a risk of impaired neurological functions (assessed by intraoperative neurophysiology).

We here present a protocol of a prospective phase II trial which for the first time evaluates the outcome of early Gamma Knife\(^8\) (Elekta AB, Stockholm, Sweden) stereotactic radiosurgery (GK-SRS) based on early postoperative imaging and tumor delineation.

STUDY GOALS AND OBJECTIVES

Hypothesis

The overall hypothesis is that, consistent with the current notion of a strong correlation of extent of resection and survival,\(^8\) an early stereotactic radiosurgery (SRS) boost to residual tumors will be beneficial after subtotal resection of GBM. The goal of this study is therefore to measure efficacy and safety of early postoperative GK-SRS to areas of residual tumor after resection of newly diagnosed GBM.

Primary Objective

- Median progression-free survival (PFS), defined as time (in months) from surgery to confirmed radiological tumor progression or death by any cause. All MRI scans will be evaluated using modified response assessment in neuro-oncology (RANO).\(^9\) If discrimination between progression and pseudoprogression cannot be made unequivocally, advanced MRI (such as perfusion imaging or spectroscopy) may be applied.\(^10\)

Secondary Objectives

- Occurrence of radiation induced acute (<3 wk), early delayed (<3 mo), and late (>3 mo post-SRS) neurotoxicity, assessed by serial neurological examinations.
- Incidence of symptomatic radionecrosis, assessed by serial MRI scans including Dynamic Susceptibility Contrast (DSC) perfusion.

STUDY DESIGN

Gamma-GBM is an open-label, single-center, prospective, single-arm phase II study. A total of 50 patients are planned to be enrolled. Estimated data completion will be in February 2020.

Inclusion Criteria

Eligible patients must be between 18 and 80 yr with a Karnofsky Performance Status of 60 or more. The histology of a GBM must be proven by intraoperative frozen section and there must be residual tumor delineable in an early-postoperative MRI (within 72 h after surgery). Written informed consent must be obtained before surgery. Patients in child-bearing ages must use adequate birth control (eg, oral contraceptives).

Exclusion Criteria

Any previous cranial radiotherapy, inconclusive histology or histology other than GBM (eg, low(er)-grade-glioma, metastasis), contraindications for radiotherapy or chemotherapy, clinically significant bleeding or clotting disorders and contraindications for computed tomography (CT) or MRI scans will result in exclusion from the trial.

Withdrawal Criteria

A patient will be withdrawn from the trial if postsurgery scans do not show areas of residual tumors, or if SRS is (technically or clinically) not possible (eg, due to unfavorable geometries, unacceptable radiation doses to risk structures, postoperative psychotic syndromes, etc). All screening failures and withdrawals where SRS was not performed will be replaced.

METHODOLOGY

Surgery

The resection is performed as standard frameless stereotactic surgery. Intraoperative application of 5-aminolevulinic acid is optional. A maximum safe resection approach is recommended, but not mandatory.

Stereotactic Radiosurgery

All patients with confirmed GBM (frozen sections) will receive an SRS planning MRI scan within 72 h postsurgery and will then undergo SRS not later than 12 h after MRI scanning as brain shifts may occur during this time (Figure). Depending on the patient’s condition and choice, mask-based or frame-based fixation can be used during SRS. In case of mask fixation, cone beam...
CT-based image guidance and infra-red-based high-definition motion management will be applied to minimize positioning uncertainties. Residual tumor will be identified by comparing native and contrast enhanced T1 MRI scans. A gross tumor volume (GTV) will then be defined that includes all lesions that are hyperintense in contrast-enhanced T1 sequences (ie, that take up contrast) but are hypointense in the native T1 sequence. In case frame-based treatment is envisaged, the planning target volume (PTV) will be the GTV. In case mask-based treatment is chosen, the PTV will be generated by isotropic expansion of the GTV by 2 mm. SRS will then be applied with a total dose of 15 Gy prescribed to the 50% isodose line.

**Adjuvant Radiochemotherapy**

Following surgery, the patient will be treated with the standard-of-care adjuvant therapy consisting of combined radio- and chemotherapy with 60 Gy external beam radiotherapy (EBRT) plus 75 mg/m²/d temozolomide daily followed by 6 cycles of 150 to 200 mg/m²/d temozolomide d1-5, q4w.

**DISCUSSION**

Prior studies have shown a clear correlation between higher radiation doses and longer survival in patients with GBM.
GK-SRS is a highly precise modality to stereotactically ablate intracranial tumors and, although the technique has been used since the 1950s, there has been a continuous improvement of precision and patient comfort up to now. Although retrospective studies on SRS in GBM suggested a benefit (15 Gy to the 50% isodose), it had no effect on outcome in the randomized RTOG 93-05 trial from the "pretemozolomide era." However, in this trial, the boost was applied 4 to 5 wk after surgery (1 wk before EBRT), when discriminating surgery-induced contrast enhancements from residual tumor areas is challenging.

Serial imaging and single-cell labeling studies suggested that the doubling time of an untreated (residual) GBM mass may be as little as few days, we hypothesize that immediate radiosurgery to areas of residual tumor could bridge the therapeutic gap between surgery and EBRT.

TRIAL STATUS

Patient recruitment started in February 2017.

SAFETY CONSIDERATIONS

As local hematomas are a possible adverse event of the screw fixation of the frame included patients must have adequate hemostasis. All patients will receive a single shot of steroids (dexamethasone) at the day of SRS to prevent mass effects.

Adverse events (AE) will be recorded continuously and classified according to Common Terminology Criteria for Adverse Event classification. AE will be monitored by serial clinical and neurological examinations as well as serial MRI scans.

Neurotoxicity will be classified as acute (if occurring < 3 wk after SRS), as early delayed (<3 mo), or as late (>3 mo post-SRS) neurotoxicity.

A specific emphasis will be put on the differentiation of pseudo-progression and "true" tumor progression. As RANO criteria do not tackle this issue adequately, we will extensively use advanced MRI imaging techniques such as DSC perfusion or spectroscopy. Radiation necrosis (RN) usually occurs delayed (6-18 mo after SRS) and may be distinguished from tumor progression by FET-PET (not mandatory). For patients with confirmed RN, bevacizumab is a treatment option that will not be considered as an event for PFS.

Serious adverse events will be reported within 24 h after knowledge to the local institutional review board (IRB).

FOLLOW-UP

Follow-up visits will be performed 6 wk after radiochemotherapy and then quarterly thereafter. All patients will receive a clinical and neurological status evaluation as per the standard of care. MRI scans will take place at all FUs with T1 +/- contrast, T2-TSE, T2-FLAIR, DWI, and DSC perfusion imaging to document tumor status and potential radiation-induced side effects. MRI scans have to be assessed using modified RANO criteria and perfusion imaging. Adverse events will be followed until they dissolved or until a stable condition has been reached.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data will be collected by instructed study investigators and stored pseudonymized electronically in compliance with local regulations for 30 yr. Full data access will be granted to supervising authorities; pseudonymized data access will be given to all persons scientifically involved in the study.

Statistical Considerations

A sample size of 50 patients with histologically confirmed GBM and delineable residual tumor was regarded sufficient to detect efficacy and safety signals. It also allows us to detect an absolute difference in the median PFS (the primary endpoint) by 6.9 to 13.8 mo (estimated hazard ratio of 0.50) compared to a historical control—the pivotal trial that established the current standard of care where patients showed a median PFS of 6.9 mo; at a 1-sided level of significance of 10% if the FU is 2 yr and 5% of patients are lost to FU.

All time-to-event endpoints will be analyzed by event rates at predefined time points and median time-to-event based on the Kaplan–Meier method. All other endpoints will be performed descriptively separately for each stage.

QUALITY ASSURANCE

This trial was not judged to require a Data Safety Monitoring Board. All adverse events exceeding CTC Grade 2 will be reported to the IRB for evaluation.

EXPECTED OUTCOMES OF THE STUDY

We expect that the immediate boost to residual tumors will improve PFS and, ultimately, patient survival. In case this single-arm trial suggests superiority of an early SRS boost in terms of PFS, a randomized trial can be conducted to generate level I evidence.

DURATION OF THE PROJECT

The estimated date of the completion of the primary outcome measures will be the beginning of 2020; the estimated study completion date will be the end of 2020. The complete study duration is estimated to be 3 to 4 yr.
ETHICS

The study is approved by Medical Ethics Committee II of the Medical Faculty Mannheim of the University of Heidelberg (2016-543N-MA) and will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. The trial is registered with clinicaltrials.gov: NCT03055208.

Disclosures

This trial is sponsored by the University of Heidelberg/University Medical Center Mannheim. Financial support was provided by ELEKTA Instrument AB, Stockholm, Sweden, the manufacturer of the Gamma Knife. Dr Wenz receives travel and research grants from ELEKTA AB. Dr Giordano received travel grants from ELEKTA AB.

REFERENCES