Trial Description

Title

Test-Retest-Reliability and Tumor-Localisation-Dependent Sensitivity of Neurocognitive Tests in Glioblastoma Patients. A prospective multicentric study.

Trial Acronym

NOA-19 (ReCog-GBM-L)

URL of the trial

http://neurochirurgie.uk-koeln.de/de/neurochirurgie/forschung/klinische-forschung/klinische-arbeitsgruppen/ag-funktionelle-bildgebung

Brief Summary in Lay Language

Brain tumours are often associated with neurocognitive deficits. Recent studies showed a high impact of neurocognitive deficits on health-related quality of life. Moreover, neurocognitive function can serve as a strong independent predictor for survival of brain tumour patients. Worsening of neurocognitive functions may even allow to detect tumour recurrencies / progression. Additional therapy such as radiotherapy or chemotherapy can influence neurocognitive functions, depending on the treatment form and dose / intensity.
Thus, investigating neurocognitive functions in brain tumour patients is highly interesting and can improve the management of those patients. However, there is no consensus regarding a practicable neurocognitive test battery for brain tumor patients available for German-speaking patients until now. Moreover, shorter test batteries specifically adapted for distinct brain tumour regions are needed, especially to allow time-efficient individual follow-up testing.
We, therefore, conduct a prospective evaluation of a novel test battery, which covers all crucial neurocognitive functions and requires roughly 45 min testing time and is paper-based.
Therefore, 250 patients with newly diagnosed monolocular, supratentorial contrast-enhancing brain tumours shall be allocated to the study (expected ratio tumor resection : stereotactic biopsy = 1:8 - 1:10). 13 university / teaching hospitals have provided written agreement to participate and are actively recruiting patients for this multicentric study.
The participation in the study does not influence the tumour treatment at all. During the patients' regular stay in the hospital (for tumour surgery), neurocognitive testing will take place once before and twice on consecutive days (day 3-7) after surgery. Moreover, follow-up testings are planned at the time points of the regular outpatients visits +/- every 3 months after surgery (as long as no tumour recurrence is detected).

Aims of the study are: (1) investing the effect of surgery (controlled for unspecific effects by comparison to the biopsy cohort) and (2) the effect of concomitant radiochemotherapy (3-months-follow-up) on neurocognitive functioning; (3) measure the test-parallel-test reliability of the test battery; (4) correlate the neurocognitive (functional) data to the individual MRI-lesions (by lesion symptom mapping).

Additional aims of the study are to validate video-assisted remote assessment

(using paper & pencil tests, provided by postal mail) as an alternative to analogue testing and to cross-validate six additional parallel test versions, which are not copyright-protected (by third parties). Herefore, data are collected from a representative collective of healthy subjects (n=192 per research question), stratified by age group, gender and educational level.

Brief Summary in Scientific Language

Brain tumours are often associated with neurocognitive deficits. However, neurocognitive functioning is still widely neglected in neurooncology as a crucial brain function for treatment response as compared to language and motor functions. Recent studies provided evidence for the impact of neurocognitive deficits on health-related quality of life (Herman et al., 2003; Meyers et al., 2003; Giovagnoli et al., 2005). Moreover, neurocognitive function can serve as a strong independent predictor for overall survival as well as progression-free survival (Daniels et al., 2011). Neurocognitive decline may even be regarded as a sensitive tool for early detection of tumour progression, prior to radiological signs (Meyers et al., 2003; Brown et al., 2006). Regarding the effects of tumour treatment on neurocognitive functions, several drugs such as Bevacizumab have been accused to cause a functional deterioration (Taphoorn et al., 2004; Friedman et al., 2009; Wefel et al., 2011; Henriksson et al., 2011). However, a consensus regarding a practicable neurocognitive test battery for brain tumour patients is missing so far and the lack of standardized neurocognitive testing is a major deficit in most clinical trials. Moreover, location-specific test batteries are needed to allow efficient testing, especially in the perioperative context.
We, therefore, conduct a prospective evaluation of a novel test battery, which covers all crucial neurocognitive functions and requires 45 min testing time. The battery consists of validated and reliable tests based on the literature and empirical validation in our multidisciplinary research group. Some tests underwent partial shortening or simplification (to avoid tiring of the tumour patients and keep the efforts to a reasonable / feasible level). The battery includes the following tests: Digit Span Test (DST), Symbol Digit Modality Test (SDMT), Hopkins Verbal Learning Test – Revised (HVLT-R), Stroop Colour Word Test, Trail Making Test (TMT) A & B, Judgement of Line Orientation Test (JLOT), 9 Hole Pegboard Test, Controlled Oral Word Association Test (COWAT), Bells Test, Rey-Osterrieth/Taylor Complex Figure Test (ROCFT), Mini Mental State Test (MMST). According to an a-priori power analysis, 250 patients with newly diagnosed monolocular, supratentorial contrast-enhancing intraaxial tumours (suspected glioblastoma) shall be allocated to the trial prior to surgical tumour removal are minimally invasive, stereotactic biopsy (expected ratio tumor resection : stereotactic biopsy = 1:8 - 1:10). To allow for faster recruitment, we chose a multicentric study approach. 13 university / teaching hospitals are actively recruiting patients and participating in the study.
The inclusion / follow-up in the study is independent from postoperative tumour treatment. The vast majority of patients is expected to receive and accomplish radiochemotherapy with concomitant Temozolomide (TMZ) (standard treatment; best medical care) within 8-10 weeks after discharge followed by adjuvant TMZ therapy. During the patients' regular stay in the hospital (for tumour surgery/biopsy), neurocognitive testing will take place once before and twice on two consecutive days after surgery (day 3-7, provided substantial recovery from surgery). Moreover, follow-up testing is planned at the time of the regular outpatients visits approximately every three months (as long as no tumour recurrence occurs). Beyond the analysis of feasibility and the generation of normative data from a distinct clinical collective (i.e., glioblastoma patients), the study design enables conclusions regarding the effect of surgery (as compared to biopsy) and concomitant radiochemotherapy (follow-up) on neurocognitive functioning as well as to measure the parallel forms reliability of the battery.

Another main objective of the study is to investigate correlations between MRI and psychometric test data. Here, lesion symptom mapping analyses (Bates et al., 2003) will be applied. The results pinpointing the correlation of a distince neurocognitive deficit (test/domain) with a specific tumour location pattern can be used to establish shorter, location-specific test batteries.

In addition to the investigations in glioblastoma patients, the neurocognitive test battery will be applied to a resprensentative collective of healthy subjects (n=192; stratified by age group, gender and educational level), including the cross-validation of six additional parallel versions which are free of copyright protection by third parties. Moreover, the remote administration of the test battery using a telemedical approach (i.e. video meeting) and the standard “paper & pencil” test material (provided by postal mail) is validated in comparison to the analogue test setting.

Do you plan to share individual participant data with other researchers?

[---]*

Description IPD sharing plan

[---]*

Organizational Data

- DRKS-ID: **DRKS00010162**
- Date of Registration in DRKS: **2016/03/24**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **14-109 , Ethik-Kommission der Medizinischen Fakultät der Universität zu Köln**

Secondary IDs

Health condition or Problem studied

- ICD10: **C71.9 - Malignant neoplasm: Brain, unspecified**

Interventions/Observational Groups

- Arm 1: **Microsurgical tumour resection (with surgical aim of complete removal of CE-lesion).**

The participation in the study does not influence the tumour treatment at all. In addition to the regular treatment and diagnostics, neurocognitive testing is performed (paper-based tests) at several times: During the patients' regular stay in the hospital (for tumour surgery), neurocognitive testing will take place once before and twice on consecutive days (day 3-7) after surgery. Moreover, follow-up testing is planned once at the time of the regular outpatients visits 3 months after surgery (+/- 4 weeks).

- Arm 2: <style fontName='DejaVu Sans' isBold='true'>Stereotactic Biopsy without relevant reduction of CE-lesion (< 10%) with surgical means</style>
- Arm 3: **Stereotactic Biopsy followed by microsurgical tumour resection (with surgical aim of complete removal of CE-lesion)**

Characteristics

- Study Type: **Non-interventional**
- Study Type Non-Interventional: **Observational study**
- Allocation: **Non-randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Other**
- Purpose: **Other**
- Assignment: **Other**
- Phase: **N/A**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

Alterations of neurocognitive functioning after brain tumour resection (vs. stereotactic biopsy). Herefore, changes of the individual test performance after surgery as compared to before surgery are assessed as changes in the test score values in % (individual level). Assessment at time points 1 vs. 3 (before surgery vs. after surgery = before discharge).

Secondary Outcome

1. Alterations of neurocognitive functioning following radiochemotherapy (individual level in %; see primary endpoint) - Assessment at visits 3 & 4.
2. Test-parallel-test-reliability of neurocognitive function assessment in glioblastoma patients (individual level; score values of each test) - Assessment at visits 2 & 3.
3. Correlation of neurocognitive deficits with tumour / oedema location (T-Scores of each test; lesion symptom mapping) - Assessment at visits 1, 3 & 4.
4. Quality of life (SF-12 Score value) - Assessment at visits 1 & 4.
5. Depression (BDI Score value) - Assessment at visits 1 & 4.

Visits: (1) before surgery, (2/3) after surgery / before discharge, (4) +/- 3 months after surgery

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Köln**
- Medical Center **Donau-Isar-Klinikum, Deggendorf**
- University Medical Center **Würzburg**
- University Medical Center **Neurooncology, Tübingen**
- University Medical Center **Regensburg**
- University Medical Center **Freiburg im Breisgau**
- University Medical Center **Heidelberg**
- University Medical Center **Düsseldorf**
- University Medical Center **Münster**
- University Medical Center **Dresden**
- University Medical Center **Mainz**
- University Medical Center **Neurosurgery, Lübeck**
- Medical Center **Neurosurgery, Schwerin**
- Medical Center **Neurosurgery, Chemnitz**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2016/04/13**
- Target Sample Size: **250**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **99 Years**

Additional Inclusion Criteria

- contrast-enhancing cerebral tumor (suspection: glioblastoma): first diagnosed, supratentorial, unilateral, single lesion (no further intracerebral tumors)
- age > 18 yrs
- written informed consent
- good clinical state (KPS 70 or better, i.e., independent in basic daily life)

Exclusion criteria

- infratentorial, multiple or bihemispheric cerebral tumors (according to CE-T1), gliomatosis cerebri
- previous brain radiation therapy
- chemotherapy within 2 yrs prior to inclusion
- non-controlled epilepsy (despite anticonvulsive drugs > 3 focal seizures per day or > 1 generalized seizure within 3 days prior to 1st neurocognitive testing).
- abuse of drugs which may alter neurocognitive functioning (incl. alcohol) other than regular pain killers or regular anticonvulsive treatment < 24 hrs. prior to neurocognitive assessment.
- severe (chronic) migraine, cluster- or other headache
- severe depression (BDI Score > 30 / 63 pts or acute/decompensated psychiatric disorder)
- severe dementia (Mini Mental State Test [MMST] < 20 / 30 pts.)
- institutionalised patients
- contraindications regarding exposition to magnetic fields (MRI scan), e.g. metallic devices

Addresses

■ **Primary Sponsor**

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Contact for Public Queries

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Sources of Monetary or Material Support

■ **Institutional budget, no external funding (budget of sponsor/PI)**

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■ **Private sponsorship (foundations, study societies, etc.)**

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Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

Status

- Recruitment Status: **Recruiting ongoing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*