Trial Description

Title

Whole-brain irradiation with hippocampal sparing and dose escalation on metastases: neurocognitive testing and biological imaging

Trial Acronym

HIPPORAD

URL of the trial

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Brief Summary in Lay Language

The standard therapy for patients with more than 3 brain metastases of solid tumors is whole-brain radiotherapy. In this case, the entire brain (metastases as well as the healthy tissue) is treated with a uniform dose. With this treatment, life expectancy can be prolonged and symptoms can be controlled. Nevertheless, a frequent side-effect is a deterioration of learning and memory that affects quality of life.
This negative effect is explained by a damage of the so-called hippocampus. The hippocampus is the brain structure that is critically involved in memory and learning, e.g. shopping lists or a person's name. Recently, a technique that spares the hippocampus during whole-brain radiotherapy has been developed and is already used in clinical practice.
The type of radiotherapy that is examined for its beneficial effects equals the standard treatment (whole-brain radiotherapy), but with sparing of the mentioned hippocampus.
We expect that this new treatment approach will preserve memory to a significantly greater extent than whole-brain radiotherapy without hippocampal sparing. Therefore, all patients enrolled in this trial will be thoroughly examined concerning their memory performance before and after the treatment.
In parallel, the existing brain metastases will be treated with a higher dose (so-called dose escalation or boost) than the surrounding healthy tissue. This is supposed to increase the local tumor control compared to standard whole-brain radiotherapy.
To reliably evaluate a beneficial effect of hippocampal sparing whole-brain radiotherapy on learning and memory, it is necessary to randomly assign the patients to predefined treatment arms. This procedure is called randomization.
In this trial, randomization in the following two treatment arms will be performed: one half of patients will be treated with hippocampal sparing whole-brain radiotherapy (experimental arm) and dose escalation to the metastases, the other half will be treated with whole-brain radiotherapy and boost on metastases but without hippocampal sparing (control group).
Furthermore, in the context of this trial, we will also evaluate whether a potential beneficial effect on memory can also be visualized by imaging. Therefore, magnetic resonance imaging (short: MRI) will be performed in this trial before and after treatment. This established imaging modality can depict brain tissue with high-resolution.

Brief Summary in Scientific Language

In patients with multiple brain metastases of solid tumors a whole brain radiotherapy (WBRT) is the most widely used treatment option and improves tumor control and overall survival. WBRT might be associated with considerable neurotoxicity and may reduce the patients' quality of life. It is known that neural stem cells are located in the hippocampal region, supporting lifelong neurogenesis. The reduction of hippo-campal functions like learning and memory as a consequence of WBRT is explained by damage to neural stem cells and by a lower ability for regeneration of neuron populations. Avoidance of neural stem cells in hippocampus may help to reduce the neurotoxicity of WBRT.
Several studies have shown that a dose escalation to the brain metastases contribute to better local tu-mor control and putatively longer overall survival. By the use of new irradiation techniques a WBRT with hippocampal avoidance and concomitant boost to the metastases (HA-WBRT) is feasible.
The current project aims to investigate the benefits of HA-WBRT compared to WBRT without hippocampal avoidance on memory performance of patients treated for brain metastases. On a second level, structural and functional changes of the brain will be investigated on MRI and FDG-PET. Moreover, the study will assess the impact of dose escalation on local tumor control and survival.
It is hypothesized that the novel, recently established technique of WBRT with dose escalation to brain metastases and hippocampal avoidance minimizes the side-effect of cognitive deterioration while at the same time providing an optimal improvement of tumor control for multiple brain metastases.
Note: The exclusion criteria were changed and updated in a protocol amendment dated 27.08.2018: EC University Medical Center Freiburg; ID 181237

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

[---]*

Description IPD sharing plan

[---]*

Organizational Data

- DRKS-ID: **DRKS00004598**
- Date of Registration in DRKS: **2016/06/02**
- 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.: **108/16 , Ethik-Kommission der Albert-Ludwigs-Universität Freiburg**

Secondary IDs

Health condition or Problem studied

- ICD10: **C71 - Malignant neoplasm of brain**

Interventions/Observational Groups

- Arm 1: **Whole brain radiotherapy (WBRT) with concomitant boost on the metastases and with hippocampal avoidance (HA).**
- Arm 2: **Whole brain radiotherapy (WBRT) with concomitant boost on the metastases without hippocampal avoidance (HA).**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **patient/subject, assessor, data analyst**
- Control: **Active control (effective treament of control group)**
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **II**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

Neurocognitive function in 3 month survivors, measured by the difference between learning performance (Verbal Learning and Memory Test) at three months after radiation therapy and at baseline

Secondary Outcome

1.Intracranial progression (local tumour progression, progression in the WBRT area without dose escalation, within hippocampus, overall; number of new cerebral metastases)
2.Extracranial progression
3.Overall survival
4.Death due to brain metastases
5.Locally progression-free survival
6.Progression-free survival
7.Changes in other cognitive performance measures
8.Depression
9.Health-related and individual quality of life
10.Morphological alterations on MRI

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Albert-Ludwigs-Universität, Freiburg im Breisgau**
- University Medical Center **Klinik für Strahlentherapie, Würzburg**
- Medical Center **GSR Hameln im Sana Klinikum Hameln-Pyrmont, Hameln**
- University Medical Center **Klinik und Poliklinik für Strahlentherapie, Regensburg**
- University Medical Center **Klinik und Poliklinik für Strahlentherapie und Radioonkologie, München; LMU**
- University Medical Center **Klinik/Poliklinik für Strahlentherapie und Radioonkologie, Dresden**
- Medical Center **Krankenhaus Nordwest GmbH Radioonkologische Klinik, Frankfurt a.M.**
- Medical Center **Klinik und Poliklinik für Strahlentherapie, München, Klinikum rechts der Isar**
- Medical Center **Klinik für Strahlentherapie, Dessau, Städt. Klinikum**
- Medical Center **Radioonkologie und Strahlenheilkunde, Bad Saarow, Helios Klinikum**
- University Medical Center **Universitätsklinikum für Radioonkologie, Tübingen**
- University Medical Center **Klinik und Poliklinik für Strahlentherapie, Köln**
- University Medical Center **Klinik für Strahlentherapie, Kiel**
- Medical Center **Radiologische Allianz Hamburg, Hamburg**
- University Medical Center **Klinik für Strahlentherapie und Onkologie, Frankfurt a.M.**
- Medical Center **Städtisches Klinikum Dresden, Dresden**
- Medical Center **Kliniken Maria Hilf, Mönchengladbach**
- Medical Center **Klinikum Wolfsburg, Wolfsburg**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2016/09/21**
- Target Sample Size: **100**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **80 Years**

Additional Inclusion Criteria

1. Patient's written informed consent has been obtained
2. Age 18-80 years, male or female
3. Legal capacity, patient is able to understand the nature, significance, and consequences of the trial
4. At least 4 brain metastases of solid tumours, with at least one, but not exceeding 10 metastases ≥ 5mm (i.e. eligible for dose escalation)
5. RPA classification I or II
6. No metastases (either preirradiated or not) and no resection cavity within the hippocampus or in a distance of 7mm to the hippocampus (= hippocampal avoidance region, HAR)

Exclusion criteria

1. Simultaneous participation in other interventional trials which could interfere with this trial
2. Participation in a clinical trial within the last thirty days before the start of this trial, previous participation (randomisation) in this trial
3. Known or persistent abuse of medication, drugs or alcohol
4. Persons who are in a relationship of dependence/employment with the sponsor or the investigator
5. Pregnancy, nursing or patient not willing to prevent a pregnancy during treatment
6. Cerebral lymphomas, metastases of germ cell tumours, SCLC
7. Acute neurological symptoms demanding an immediate start of RT
8. CNS diseases or syndromes accompanied by cognitive deficits or radiological changes of the brain, e.g., dementia, major depression, clinically manifest hypertensive encephalopathy, meningiosis carcinomatosa
9. Previous brain irradiation (SRS/SFRT) of >1 brain metastasis >3cm or >3 brain metastases >1cm each
10. Previous brain irradiation <3 months before start of treatment
11. Previous surgical resection (± adjuvant SFRT) of >1 brain metastasis (biopsy allowed)
12. Previous surgical resection of 1 brain metastasis <4 weeks before start of treatment
13. Uncontrolled pretreated brain metastasis/-es after SRS/SFRT
14. Last application of chemotherapy/immunotherapy/targeted therapy <1 week before randomisation
15. RT planning conforming to OAR constraints not feasible (including previous cranial irradiation)
16. Benzodiazepines, barbiturates, topiramate, hydantoine as antiepileptic medication
17. > 1 brainstem metastasis ≥5mm
18. Brainstem metastasis >2cm
19. Brain metastasis >3.5cm
20. Resection cavity eligible for dose escalation >3.5cm

Addresses

■ **Primary Sponsor**

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■ **Contact for Scientific Queries**

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Sources of Monetary or Material Support

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

Deutsche Krebshilfe e.V.
Buschstr. 32

Private sponsorship (foundations, study societies, etc.)

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

Status

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

Trial Publications, Results and other documents

Please note:
There are additional attributes available concerning this trial. To open an extended view please click here.