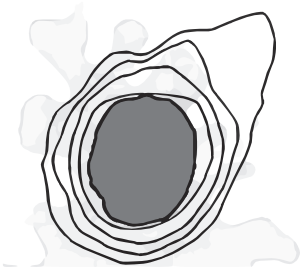
FSRT Trial
Study Synopsis



Efficacy and Safety of Fractionated Stereotactic Radiation Therapy versus Single Fraction Stereotactic Radiosurgery for Large Brain Metastases

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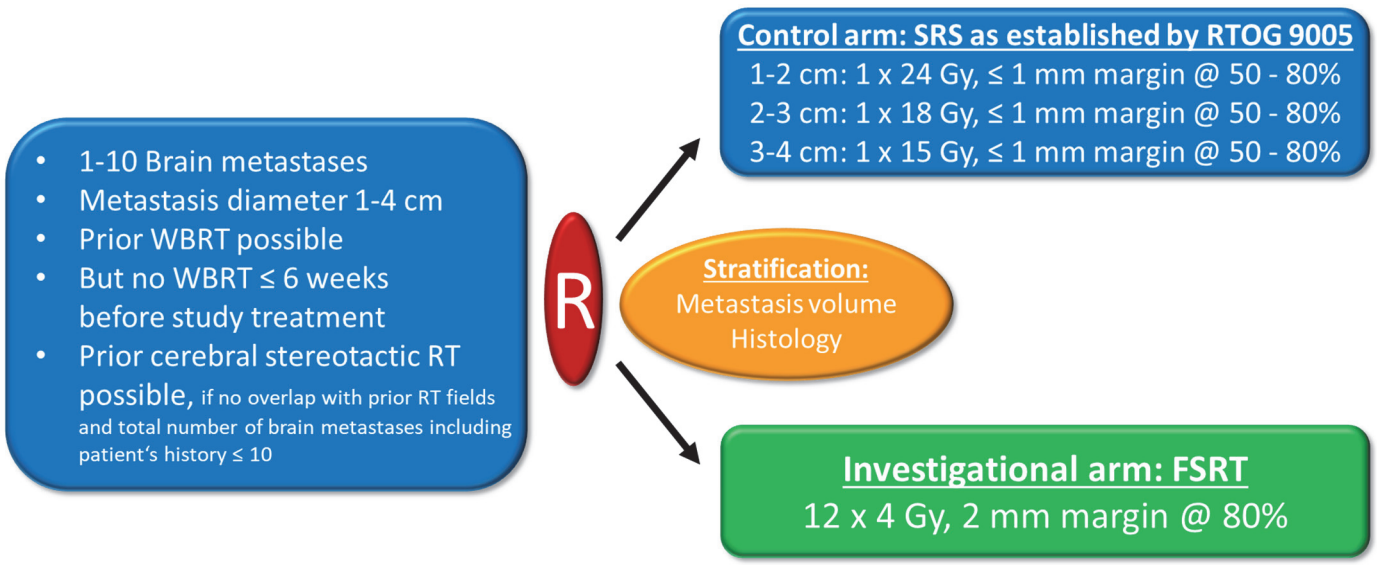
FSRT TRIAL SYNOPSIS

Protocol title	Efficacy and Safety of Fractionated Stereotactic Radiation Therapy versus Single Fraction Stereotactic Radiosurgery for Large Brain Metastases
Study design	Prospective, multicenter randomized clinical trial with stratification by metastasis volume and histology
Clinical indication	Brain metastases from solid tumors
Rationale	There is a growing need for safe and efficacious treatment of brain metastases. However, evidence for optimal treatment of larger brain metastases is poor. The current gold standard for radiotherapy of large brain metastases is single-session radiosurgery (SRS), as defined by RTOG 9005. However, available evidence suggests that fractionated stereotactic radiotherapy (FSRT) could be significantly superior in terms of local control and toxicity in the subset of larger brain metastases. Fractionated stereotactic radiotherapy (FSRT) is routinely used in clinical practice but has never been tested against single-fraction radiosurgery (SRS) in a randomized controlled trial so far. This study was therefore designed to determine whether FSRT with a dose of 12 x 4 Gy and a 2-mm safety margin is superior to single-fraction SRS according to RTOG 9005 criteria (gold standard) for the treatment of large brain metastases in terms of tumor control and CNS side effects.
Primary objective	Improvement of local control of irradiated brain metastases Primary endpoint: Time to local progression - *TTLP* Local progression will be defined according to the *RANO-BM* criteria by an increase of at least 20% in the longest diameter of the metastasis relative to nadir or baseline. In addition to the relative increase of 20% the lesion must increase by an absolute value of 5 mm or more. True local progression and radionecrosis are differentiated via a prespecified algorithm in the trial. If multiple metastases are treated in the trial, progression is defined as at least one metastasis fulfilling the criteria for progression.
Secondary objectives	Improvement of the tolerability of local radiotherapy, as measured based on the endpoints CNS toxicity and, in

	particular, radiation necrosis in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Improved tolerability will also be measured as time to radiation necrosis. Improvement of the local control of irradiated brain metastases, as determined based on volumetric criteria. Volumetric criteria may have important methodological advantages over traditional endpoints for the identification of treatment failure, especially in the case of large brain metastases. This study aims to improve our understanding of volumetric criteria and helps to further establish them. Quality of Life (EORTC QLQ-C30 and QLQ-BN20) Improvement of local progression-free survival Improvement of overall survival Improvement of brain metastases-specific survival Time to distant brain failure
Translational research projects	Differentiation of radiation necrosis from recurrent metastasis based on conventional MRI-imaging using advanced pattern-recognition and machine learning techniques. (*Radiomics* project: *DEEP-CER-DIFF*). Correlation of *individual radiosensitivity* and radiation-related toxicity especially radionecrosis after stereotactic radiotherapy of brain metastases. *Detailed Immunophenotyping* to investigate systemic immune reactions following stereotactic radiotherapy of brain metastases.
Main inclusion criteria	Age ≥ 18 years, no upper age limit. Karnofsky Performance Scale (KPS) score > 50, Life expectancy ≥ 3 months. 1-10 brain metastases from a solid cancer except small cell lung cancer and germinomas. Indication for local radiotherapy of one or more brain metastases measuring 1 to 4 cm in longest diameter (measured in transversal, sagittal, coronal or oblique planes, the longest diameter measured in any plane counts)

Main exclusion criteria	Whole-brain radiotherapy completed ≤ 6 weeks before study treatment or planned whole-brain radiotherapy following local radiotherapy. Prior radiotherapy of the metastasis or metastases to be irradiated in the present study. Relevant overlap of prior radiotherapy fields, cerebral or otherwise, with the metastasis or metastases to be irradiated in the present study Location of metastasis to be irradiated in the brainstem. Total of > 10 brain metastases, including previous metastases, at the time of inclusion in the study. Contraindication for cerebral MRI.
Time schedule	Start of study: Q3 2020 Start of recruitment: Q1 2021 Duration of recruitment: 3 years Follow-up period: 2 years End of study: 2026
Sample size	382 patients 191 control arm (SRS) 191 investigational arm (FSRT)
Randomization	1 (control arm): 1 (experimental arm) Randomization will be conducted at the patient level.
Treatment	Control arm: Single-fraction stereotactic radiosurgery (SRS) with a total dose of 1×24 Gy (∅ 1-2 cm), 1×18 Gy (∅ 2-3 cm) or 1×15 Gy (∅ 3-4 cm), respectively, delivered to the metastasis according to RTOG 9005 guidelines (gold standard) including a margin of up to 1 mm depending on institution-specific accuracy. Experimental arm: Fractionated stereotactic radiotherapy (FSRT) with a total dose of 48 Gy in 12 fractions of 4 Gy each, with a safety margin of 2 mm
Follow-up	Until 2 years after treatment Initially, 6 weeks and 3 months after completion of radiotherapy (for detection of early treatment failure), then once every 3 months. Follow-up is performed for progression/radionecrosis as well as for overall survival, toxicity and distant progression, respectively.
Financing	This study is funded by the German Cancer Aid (Deutsche Krebshilfe, 70113619) and is partly financed by Universitätsklinikum Erlangen (University Hospital of Erlangen).

FSRT TRIAL STUDY FLOW CHART



Central neuroradiological review

1° Endpoint:

- Time to local progression ***(RANO-BM Criteria)***

2° Endpoints:

- CNS Toxicity ***(≥ WHO °I CTCAE 5.0)***
- Radionecrosis ***(≥ WHO °I CTCAE 5.0)***
- Local Control ***(Volumetric RANO-BM Criteria)***
- Quality of Life (***EORTC QLQ-C30 and QLQ-BN20***)
- Local recurrence-free survival
- Overall survival
- Brain metastases-specific survival
- Time to distant brain failure

FSRT TRIAL EXAMINATION SCHEDULE

	Screening	Last RT	Time after completion of radiotherapy (RT)								
Assessment	**≤ 4 weeks before the start of RT**		**6 weeks**	**3 months**	**6 months**	**9 months**	**12 months**	**15 months**	**18 months**	**21 months**	**24 months**
MRI	•[a)]		•	•	•	•	•	•	•	•	•
ECOG / KPS	•	•	•	•	•	•	•	•	•	•	•
Toxicity according to NCI CTCAE v. 5.0	•	•	•	•	•	•	•	•	•	•	•
EORTC QLQ-C30	•	•	•	•	•	•	•	•	•	•	•
EORTC QLQ-BN20	•	•	•	•	•	•	•	•	•	•	•
Documentation of glucocorticoid dose	•	•	•	•	•	•	•	•	•	•	•
Documentation of systemic treatment	•	•	•	•	•	•	•	•	•	•	•
Assessment of RPA and GPA score	•										
Informed Consent	•										
Pregnancy test[b)]	•										
Planning CT	•										
Blood sample for translational research	•		•		•						

a) Time from MRI to start of radiotherapy has to be ≤ 14 days b) In females of childbearing potential: Serum β-HCG

If one follow-up examination is delayed, the date of the next follow-up examination should not be postponed but should be conducted at the specific prespecified date following radiotherapy.