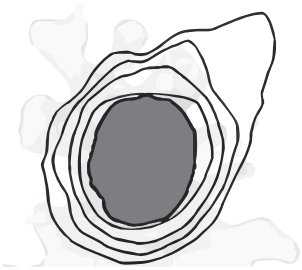
FSRT Trial
Study Protocol



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

Principal Investigator:	Prof. Dr. med. Rainer Fietkau, Strahlenklinik, Universitätsklinikum Erlangen
Scientific Study Director:	PD Dr. med. Florian Putz Strahlenklinik, Universitätsklinikum Erlangen
Study coordination:	Studiensekretariat Strahlenklinik, Universitätsklinikum Erlangen
Biometrics:	Dr. Axel Hinke CCRC, Düsseldorf
Translational Research:	Prof. Dr. Udo Gaipl Strahlenklinik, Universitätsklinikum Erlangen

Protocol code:	FSRT Trial
Protocol version:	Protocol version 1.7, 02.12.2022

supported by Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

PERSONS AND INSTITUTIONS WITH LEAD RESPONSIBILITY

Principal Investigator / Study Director:

Prof. Dr. med. Rainer Fietkau
Strahlenklinik
Universitätsklinikum Erlangen
Universitätsstraße 27
91054 Erlangen
Tel.: 09131/85-33968
Fax: 09131/85-33996
Email: rainer.fietkau@uk-erlangen.de

Scientific Study Director:

PD Dr. med. Florian Putz
Strahlenklinik
Universitätsklinikum Erlangen
Universitätsstraße 27
91054 Erlangen
Tel.: 09131/85-33968
Fax: 09131/85-39335
Email: florian.putz@uk-erlangen.de

Study Coordinator:

Studiensekretariat
Strahlenklinik
Universitätsklinikum Erlangen
Universitätsstraße 27
91054 Erlangen
Tel.: 09131/85-33968
Fax: 09131/85-33996
Email: st-studiensekretariat@uk-erlangen.de

Reference Center for Neuroradiology:

Prof. Dr. med. Arndt Dörfler
Abteilung für Neuroradiologie
Universitätsklinikum Erlangen
Schwabachanlage 6
91054 Erlangen
Tel.: 09131/85-33968
Fax: 09131/85-39335
Email: arndt.dörfler@uk-erlangen.de

Translational Research:

Prof. Dr. Udo Gaipl
Strahlenklinik
Strahlenimmunbiologie
Universitätsklinikum Erlangen
Universitätsstraße 27
91054 Erlangen
Tel.: 09131/85-44258
Fax: 09131/85-39335
Email: udo.gaipl@uk-erlangen.de

Biostatistics:

Dr. Axel Hinke
CCRC
Elly-Heuss-Knapp-Str. 36
40595 Düsseldorf
Tel.: 0211/7000675
Fax: 0211/7004196
Email: axel.hinke@hotmail.de

Data monitoring:

Winicker Norimed GmbH Medizinische Forschung
Deutschherrnstraße 15-19
90429 Nürnberg
Tel.: 0911-92680-0
Fax: 0911-92680-8839
Email: wn@winicker-norimed.com

Data Safety Monitoring Board

Radiotherapy:
Herrmann, Thomas, Prof. Dr. med.
Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Strahlentherapie und Radioonkologie
Fetscherstr. 74, 01307 Dresden

Baumann, Michael, Prof. Dr. med.
Deutsches Krebsforschungszentrum in der Helmholtz-Gemeinschaft
Im Neuenheimer Feld 280, 69120 Heidelberg

Neurosurgery:
Schackert, Gabriele, Prof. Dr. med.
Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Neurochirurgie
Fetscherstr. 74, 01307 Dresden

Medical Oncology:
De Wit, Maike, Prof. Dr. med.
Vivantes Klinikum Neukölln, Klinik für Innere Medizin - Hämatologie, Onkologie und Palliativmedizin
Rudower Straße 48, 12351 Berlin Neukölln

Ethics:
Marckmann, Georg, Prof. Dr. med.
Ludwig-Maximilians-Universität München, Institut für Ethik, Geschichte und Theorie der Medizin
Lessingstraße 2, 80336 München

Statistics:
Martus, Peter, Prof. Dr. rer. nat.
Universitätsklinikum Tübingen, Institut für Klinische Epidemiologie und angewandte Biometrie
Silcherstraße 5, 72076 Tübingen

PROTOCOL APPROVAL – SIGNATURES

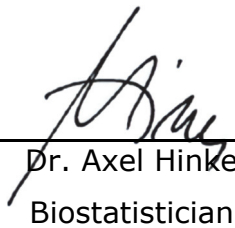
02.12.2022
Date

Prof. Dr. Rainer Fietkau
Principal Investigator

02.12.2022
Date

Dr. Florian Putz
Scientific Study Director

02.12.2022
Date



Dr. Axel Hinke
Biostatistician

Index of Contents

ABBREVIATIONS

Computed tomography	CT
Clinical Target Volume	CTV
Dose-volume histogram	DVH
Fractionated stereotactic radiotherapy	FSRT
Graded Prognostic Assessment (score)	GPA
Gross Tumor Volume	GTV
Gray = 1 Joule / Kilogram	Gy
Image guided radiotherapy	IGRT
Karnofsky performance status scale	KPS
Magnetic resonance imaging	MRI
Planning Target Volume	PTV
Recursive partitioning analysis (score)	RPA
Radiotherapy	RT
Tumor control probability	TCP
Stereotactic radiosurgery	SRS
Whole-brain radiotherapy	WBRT

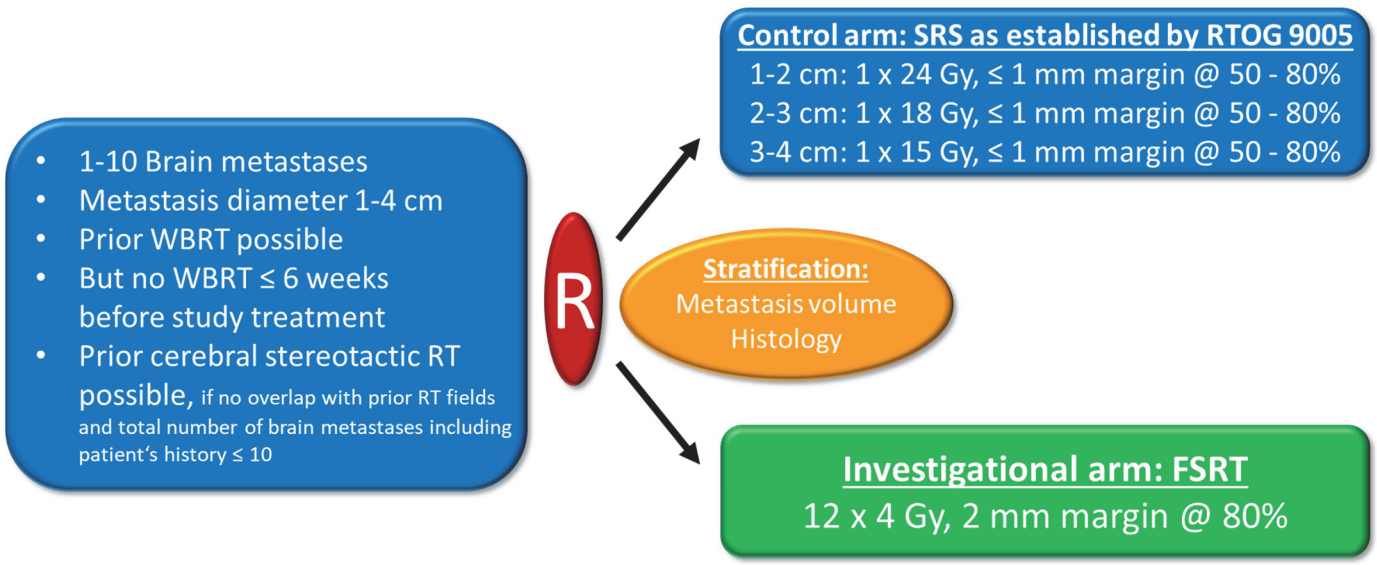
FSRT TRIAL SYNOPSIS

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

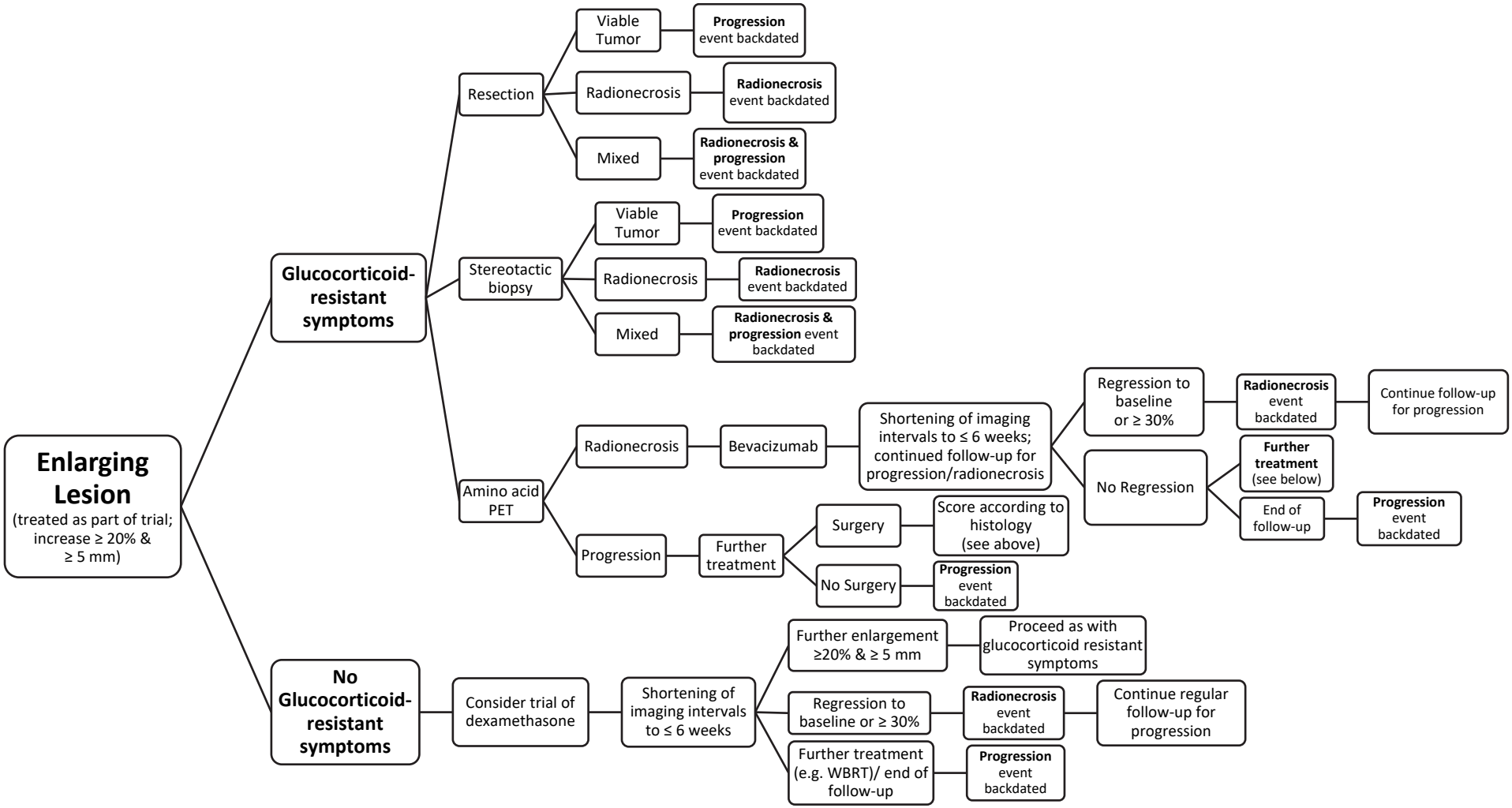
FSRT TRIAL EXAMINATION SCHEDULE

	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.

FSRT TRIAL ALGORITHM IN CASE OF AN ENLARGING LESION



This graphical representation is a high-level overview of section 7.4. Please kindly see section 7.4 for details. When the study follow-up for progression / radionecrosis ends, then follow-up for overall survival, toxicity and distant progression should continue and treatment outside of the study (e.g., for progression) should be performed at the discretion of the treating physician.

1. Scientific Background and Rationale

1.1. Scientific Background

Advances in the systemic control of metastatic cancer make it more and more important to improve the efficacy and tolerability of local radiotherapy for the treatment of brain metastases. It can be assumed that patients will require local radiotherapy for an increasing number of cerebral metastases during the course of their illness (Badiyan et al. 2016). Since the risk of treatment failure and side effects increases exponentially with the number of metastases, it is essential that the administered type of local radiotherapy be as effective and tolerable as possible.

Therapeutic options besides radiotherapy in patients with brain metastases include first and foremost neurosurgical resection. Pharmacological treatment of brain metastases can still be regarded as experimental in most cases due to the special pharmacokinetic considerations of drug delivery to the brain (Soffietti et al. 2017).

Because they are non-invasive and yet highly effective, radiotherapy modalities are of great clinical significance to the treatment of brain metastases. Therefore, neurosurgical resection is usually only indicated when decompression is necessary or when tissue specimens are needed for histologic diagnosis (Soffietti et al. 2017).

Whole-brain radiotherapy (WBRT), a procedure involving irradiation of the entire cranial vault or neurocranium, is a radiotherapeutic option that has been available since the 1950s (Chao et al. 1954). Stereotactic radiotherapy is a more recent treatment modality made available by technological advances. In stereotactic radiotherapy, local radiation is delivered directly to the brain metastases very accurately and precisely (i.e., stereotactically), with or without a safety margin of only a few millimeters. As clear evidence has emerged that WBRT may be associated with the worsening of neurocognitive function, clinicians are increasingly reserved about using it (Brown et al. 2016).

However, foregoing adjuvant WBRT not only greatly reduces the efficacy of local radiotherapy, but also increases the risk of developing new cerebral metastases (Aoyama et al. 2006, Kocher et al. 2011, Brown et al. 2016). This increases the need to improve local radiotherapy even more.

In local stereotactic radiotherapy of brain metastases, the total dose of radiation may be delivered as one single dose in a single session or as multiple fractionated doses in multiple sessions, constituting either single-fraction stereotactic radiosurgery (SRS) or fractionated stereotactic radiation therapy (FSRT), respectively (Soffietti et al. 2017).

As single-fraction stereotactic radiosurgery is the first and foremost modality investigated in prospective studies on the treatment of brain metastases to date, it is an integral part of national and international treatment guidelines (Shaw et al. 2000, Aoyama et al. 2006, Kocher et al. 2011, Brown et al. 2016). Evidence for fractionated stereotactic radiation therapy, on the other hand, is much scarcer and, for the most part, derives from a few heterogeneous retrospective studies. No randomized controlled trial (RCT) comparing SRS with FSRT exists so far. Due to the scarcity of evidence for FRST, most national and international guidelines recommend SRS as the primary or only option for the treatment of brain metastases, but some advocate FSRT as an alternative to SRS for metastases > 3 cm due to its implicit advantages (Tsao et al. 2012, Kocher et al. 2014, AWMF 2015, Soffietti et al. 2017, NCCN 2021).

1.2. Single-fraction SRS according to RTOG 9005 as the standard for local radiotherapy of brain metastases

Single-fraction stereotactic radiosurgery (SRS) according to RTOG 9005 continues to be the international gold standard for local radiotherapy of brain metastases. RTOG 9005 was a dose-finding study by the Radiation Therapy Oncology Group (RTOG), which investigated different radiation doses of increasing sizes for the treatment of brain metastases. These investigators only dosed to the edges of metastases without a safety margin (Shaw et al. 2000).

A crucial finding of the study was that side effects, especially radionecrosis, increase dramatically with the diameter of the irradiated metastasis and in the absence of dose reduction. The international recommendation derived from this study is, therefore, to irradiate brain metastases ≤2 cm in diameter with a single dose of 24 Gy, metastases measuring 2-3 cm with 18 Gy, and metastases 3-4 cm with only 15 Gy. This rule does not provide for a safety margin, which might otherwise be used, for example, to include the microscopic tumor extent or to compensate for potential inaccuracies in patient positioning or in the overall radiation planning process; moreover, the unfavorable association between irradiation volume and the risk of radionecrosis can limit the possibility of using a safety margin in single-session stereotactic radiosurgery (Shaw et al. 2000, Kocher et al. 2014).

Radionecrosis is currently the most important side effect of stereotactic brain irradiation. Radionecrosis occurs as a result of radiation damage to normal brain tissue and can lead to problems ranging from asymptomatic image morphological changes in MRI alone to life-threatening complications (Soffietti et al. 2017).

Given that the number of brain metastases treated by local radiotherapy in individual patients is rising and because the risk of radiation side effects and treatment failure increases with the number of metastases treated, it is

crucial to improve both the efficacy and the tolerability of radiotherapy simultaneously.

1.3. Rationale for hypothesizing the superiority of FSRT for the treatment of large brain metastases (1 to 4 cm)

Multiple lines of evidence suggest that fractionated stereotactic radiotherapy may be superior to single-dose stereotactic radiosurgery according to RTOG 9005 in terms of local control and side effects, especially for large brain metastases measuring 1 to 4 cm in diameter:

1. Delivery of a higher biologically effective dose:
   Wiggenraad and colleagues (2011) conducted a review of the available (mostly retrospective) literature and found that the chances of achieving local control of brain metastases depends on the biologically effective dose (BED) delivered to the tumor, based on an α/β ratio of 12 ($BED_{12\text{-}LQC}$) according to the LQC model (Wiggenraad et al. 2011).
   This shows that brain metastases are basically very radiosensitive and implies that, by means of radiation dose fractionation, it should be possible to deliver a significantly higher biologically effective dose to the tumor with the same or better tolerability. (see also Figure 1) Calculations based on the LQC model (Joiner 2009) show that a significantly higher $BED_{12\text{-}LQC}$ can be achieved by using a 12 x 4 Gy scheme compared to a single dose of 18 Gy according to RTOG 9005, corresponding to 62.8 Gy vs. 36 Gy (Wiggenraad et al. 2011).

2. Lower risk of radiation necrosis:
   Healthy brain tissue has an especially high capacity to repair damage from low single doses of radiation (Kondziolka et al. 2015).
   Consequently, the use of lower doses in FSRT allows the normal tissue to repair radiation damage between treatment sessions und increases the tolerability of treatment. Radiotherapy studies for large resection cavities after metastasis resection have already shown that fractionated delivery reduces the risk of radiation necrosis compared to single-session treatment (Amsbaugh et al. 2015, Eaton et al. 2015).

   FSRT differs from SRS in that its therapeutic selectivity is not based solely on geometric precision, but also on fundamental radiobiological differences between metastases and normal brain tissues.

3. Potential of a safety margin to prevent marginal recurrences
   Because FSRT delivers the total radiation dose more sparingly over several sessions, larger volumes can be treated without a dramatic increase in the incidence of radiation necrosis (Eaton et al. 2015). This makes it possible to include a 2-mm wide safety margin around the metastasis in addition to irradiating the metastasis volume itself. The safety margin can compensate for proven sources of residual uncertainty associated with factors ranging from patient positioning and irradiation to MRI distortion, uncertainties associated with MRI-

CT image fusion, and anatomical changes that occur between imaging and irradiation sessions. Moreover, in several neuropathological studies, investigators have observed relevant microscopic infiltration of tumor cells into surrounding brain tissues (Baumert et al. 2006, Berghoff et al. 2013). FSRT may also be able to capture this problem, which might be more pronounced in patients with larger brain metastases.

4. Further potential advantages of dose fractionation:
   In FSRT, random positioning errors are averaged out because only a fraction of the total radiation dose is applied in each treatment session. Radiation dose fractionation is also described to have other positive effects, such as reoxygenation: Some studies have shown that the large hypoxic tumors reoxygenate and thus become more radiosensitive between radiotherapy sessions; these effects could add up to additional benefits of dose fractionation, particularly in patients with large brain metastases (Kallman 1972, Withers 1975).

1.4. Rationale for a randomized controlled trial comparing SRS according to RTOG 9005 (gold standard) versus FSRT with 12 x 4 Gy

In summary, both stereotactic radiosurgery and fractionated stereotactic radiotherapy are common standard treatments for the treatment of patients with brain metastases. However, no randomized controlled trial comparing FSRT with SRS has been performed so far, and prospective studies investigating either FSRT or SRS for the treatment of large brain metastases are still scarce. Although single-session SRS according to RTOG 9005 guidelines continues to be the international gold standard for local irradiation of brain metastases (Shaw et al. 2000), significant evidence suggests that FSRT is superior, especially for the treatment of large brain metastases (Soffietti et al. 2017). What makes the present research project very important is that it is the first RCT to compare SRS with FSRT and, thus, has the potential to change the international gold standard.

Tables 1 and 2 summarize the currently available empirical evidence for the treatment of brain metastases measuring 2 to 4 cm in diameter. Consistent with claims of the superiority of FSRT, the available retrospective studies on the treatment of brain metastases with diameters of 2 to 4 cm show that SRS achieves a mean local control rate of only 55.8% compared to a mean local control of 77.0% with FSRT (Table 1, Table 2). Regarding brain metastases measuring 1 to 2 cm in diameter a similar difference in local control can be assumed, as a large volumetric study found a one-year local control for SRS of 70.2% vs. 55.6% for FSRT in brain metastases with a median diameter of 1.25 cm (Putz et al. 2020).

In addition to the available retrospective evidence in larger brain metastases, the important dose-response relationship described by Wiggenraad and Zindler for brain metastases also predicts FSRT to be superior to SRS. Figure 1 shows the relationship between the delivered $BED_{12\text{-}LQC}$ and local control at 12 months, as determined by Wiggenraad and

co-workers (Wiggenraad et al. 2011). The control arm will receive a $BED_{12\text{-}LQC}$ of 36 Gy in a single fraction of 18 Gy, and the experimental arm will receive a $BED_{12\text{-}LQC}$ of 62.8 Gy in multiple fractions (12 x 4 Gy fractionation scheme). Based on the dose-response relationship found by Wiggenraad and Zindler, this should result in a local control rate of 67.1% in the control arm and 85.8% in the experimental arm (Wiggenraad et al. 2011, Zindler et al. 2018) (Figure 1).

When combining the available retrospective evidence and the established relationship between dose and tumor control, a local control rate at 12 months of around 65% and 80% for SRS and FSRT, respectively serve as reasonable estimates for sample size calculation in a randomized trial.

This difference becomes even more clinically significant, as the number of treated brain metastases increases. For example, the probability of controlling all metastases in a patient with 4 brain metastases would be at least $(0.65)^4$ = 17.9% and could be increased to at least $(0.80)^4$ = 41.0%.

Consequently, local control of brain metastases is an important endpoint.

A variety of different FSRT schemes for brain metastases have been published. They differ, in particular, in terms of the fraction sizes used. In this research project, we deliberately used smaller dose fractions because the study objective is not only to examine a concrete FRST scheme, but also to test the basic hypothesis that FRST will result in improved tumor control while reducing side effects due to the effects of radiation dose fractionation and the use of smaller dose fractions. The initiators of this study concept are convinced that this will yield the greatest scientific knowledge gain and that, in view of future improvements in the systemic control of tumor diseases, optimal efficacy and tolerability of local brain radiotherapy should receive a higher priority than treatment time. Consistent with the basic rules of radiobiology, investigators have also shown that a single dose of 4 Gy results in a much lower radionecrosis rate than less fractionated regimens (Fokas et al. 2012, Minniti et al. 2016).

1.5. Additional scientific gain through accompanying research projects

In addition to using conventional criteria to define treatment response and progression according to the *RANO-BM* criteria (Lin et al. 2015), which are based on unidimensional measurements, the trial also includes a volumetric analysis of all metastases treated as a secondary endpoint. Volumetric analysis may have significant methodological advantages over unidimensional methods for the detection of early treatment failure, especially in the case of large metastases with complex configurations (Lin et al. 2015, Oft et al. 2020, Putz et al. 2020). Consequently, this study should contribute to improving and further establishing knowledge about volumetric criteria. The volumetric assessment and evaluation of MRI data will be carried out in collaboration of the department of radiooncology and the neuroradiological reference center at the University hospital Erlangen.

This research project will be flanked by accompanying studies that will not place any burden on the patient. They should also be of great importance and contribute to maximizing scientific-medical knowledge gain through the methods of prospective data collection. The accompanying studies to be performed are listed below:

- **DEEP-CER-DIFF**
  Radionecrosis is the most important side effect of cerebral radiotherapy and occurs at a frequency of 5-20% following SRS of larger brain metastases (Shaw et al. 2000). Radiologic imaging in radionecrosis is characterized by an increased contrast-enhancement just like in a recurring brain metastasis. Differentiation between radionecrosis and a progressive brain metastasis thus poses a challenge in clinical practice since the treatments of these two entities are diametrically opposed to each other with recurring metastasis even being an indication for re-irradiation (Soffietti et al. 2017).
  Radiomics is an innovative and promising field in medical image analysis using highly developed data processing and machine learning models such as virtual neural networks. *Radiomics* promises to reveal patterns and profound insights that are impossible to detect by a human investigator.
  As an example, it was shown recently that through *Radiomics* molecular characteristics of gliomas like IDH-1 mutation and MGMT promotor methylation could be predicted from conventional MRI sequences (Arita et al. 2018, Xi et al. 2018).
  The aim of the adjunct research project *DEEP-CER-DIFF* is therefore to investigate the potential provided through the enormous progress made in machine learning for the classification problem of differentiating radionecrosis from recurring metastases based on conventional MRI imaging.

- **Role of individual radiosensitivity in radionecrosis:**
  Each person has a unique individual radiosensitivity level, which varies by a factor of 2 in the so-called "normal" radiosensitivity range. Furthermore, some individuals have increased radiosensitivity and are even more sensitive by a factor of 2 than the average radiosensitive patient. The average radiosensitivity of tumor patients is basically similar to that of healthy individuals except that 5 to 20 percent of tumor patients have significantly increased radiosensitivity, depending on how the threshold value is set. Increased radiosensitivity could contribute to the occurrence of adverse events following radiotherapy for brain metastases. Consequently, the objective of this accompanying study is to measure individual radiosensitivity in brain metastasis patients before treatment and to correlate it with the incidence of side effects after treatment. This may answer the question whether individual radiosensitivity is related to unwanted side effects in the treatment of brain metastases and shed light on the impact of the different dose schedules used. This adjunct research project may provide important fundamental knowledge on individual dose prescription in radiooncology.

The G0 three-color fluorescence in situ hybridization (FISH) system will be used to determine individual radiosensitivity. This assay requires a 10ml whole blood sample, which is divided into two parts. One part is irradiated with 2 Gy (test) and the other is not (control). After 47 hours of culture in media to stimulate lymphocyte proliferation, the cell cycle is stopped during mitosis. As this FISH assay labels the three largest chromosomes in three different colors, approximately 25% of the DNA of a cell can be examined for chromosome aberrations. The threshold for increased radiosensitivity is defined as an average of 0.55 chromosomal breaks from aberrations. Before the start of radiation treatment, all patients will be tested by this method and divided into three radiosensitivity groups: radioresistant, normal (average radiosensitivity) and radiosensitive (increased radiosensitivity)(Distel et al. 2006). Once side effects data has been gathered, it will be analyzed to determine whether CNS-toxicity especially radionecrosis occurs more frequently in the radiosensitive group than in the other two groups.

- **Detailed Immunophenotyping**
  A local inflammatory response with invasion of macrophages and lymphocytes as well as the expression of pro-inflammatory cytokines like IL-1α, IL-6 and TNF-α is a fundamental characteristic in the pathogenesis of radiation necrosis (Furuse et al. 2015, Yang et al. 2018). The aim of the adjunct research project immunophenotyping (IPT) is to investigate systemic immunological processes following stereotactic radiotherapy of brain metastases and radionecrosis, to find possible predictive changes in immunological parameters for differentiating radionecrosis and metastatic recurrence and to correlate imaging data (*Radiomics* project – DEEP-CER-DIFF) with the changes in immunological parameters found. An assay for detailed immunophenotyping of blood will be used, which allows the characterization of 34 different immune cell subsets with use of 2.0 ml of whole blood (Rühle et al. 2016). In a currently active trial investigating patients with glioblastoma (IMMO-GLIO-01 trial, NCT02022384), we were able to show systemic immunological changes following cerebral radiation using detailed immunophenotyping of blood (Rühle et al. 2017). Furthermore, we identified by immunophenotyping that pre-therapeutically low basophil counts predicted a high-risk for HCMV-associated encephalopathy during radiochemotherapy in brain tumor patients within the GLIO-CMV-01-study (ClinicalTrials ID: NCT02600065) (glioblastoma: P = 0.002, NSCLC: P = 0.02). Moreover, this method of IPT is currently used in further active trials concerning patients with pancreatic cancer (CONKO-007 trial, NCT01827553), head-and-neck tumors (DIREKHT trial, NCT02528955; CheckRad-CD8 trial, NCT0342665; IMPORTANCE trial, NCT03386357), and solid tumurs treated with immune checkpoint inhibitors (ST-ICI trial; NCT03453892).

Table 1: Available studies on efficacy of SRS for the treatment of large brain metastases

Study	Observed local control (12 months)	Administered dose	Administered $BED_{12\text{-}LQC}$	Median diameter of the irradiated metastases
(Vogelbaum et al. 2006)	**49.0%**	1 x 18 Gy	**36.00**	> 2 cm
(Vogelbaum et al. 2006)	**45.0%**	1 x 15 Gy	**28.54**	> 3 cm
(Chao et al. 2008)	**62.0%**	1 x 18 Gy	**36.00**	> 2 cm
(Molenaar et al. 2009)	**65.0%**	1 x 18 Gy	**36.00**	> 2 cm
(Molenaar et al. 2009)	**37.0%**	1 x 15 Gy	**28.54**	> 3 cm
(Minniti et al. 2016)	**77.0%**	1 x 18 Gy	**36.00**	2.56 cm (calculated from volume)
Mean local control	**55.8 %**			

Table 2: Available studies on efficacy of FSRT for the treatment of large brain metastases

Study	Observed local control (12 months)	Administered dose	Administered $BED_{12\text{-}LQC}$	Median diameter of the irradiated metastases
(Ernst-Stecken et al. 2006)	**76.0%**	5 x 6 Gy	**43.33**	2.27 cm
(Narayana et al. 2007)	**70.0%**	5 x 6 Gy	**43.33**	3.5 cm (mean)
(Higuchi et al. 2009)	**76.0%**	3 x 10 Gy	**50.37**	3 - 4.5 cm
(Fokas et al. 2012)	**71.0%**	10 x 4 Gy	**52.35**	2.25 cm (calculated from volume)
(Matsuyama et al. 2013)	**85.2%**	BED_{10} 78.9 Gy (LQ model)	**67.16**	> 2 cm
(Kim et al. 2011)	**69.0%**	6 x 6 Gy	**52.00**	2.0 cm
(Minniti et al. 2016)	**91.0%**	3 x 9 Gy	**43.88**	2.88 cm (calculated from volume)
Mean local control	**77.0%**			

Figure 1: Available studies on stereotactic radiotherapy for brain metastases: Association between delivered $BED_{12\text{-}LQC}$ and local control at 12 months (adopted and extended from Wiggenraad et al.)

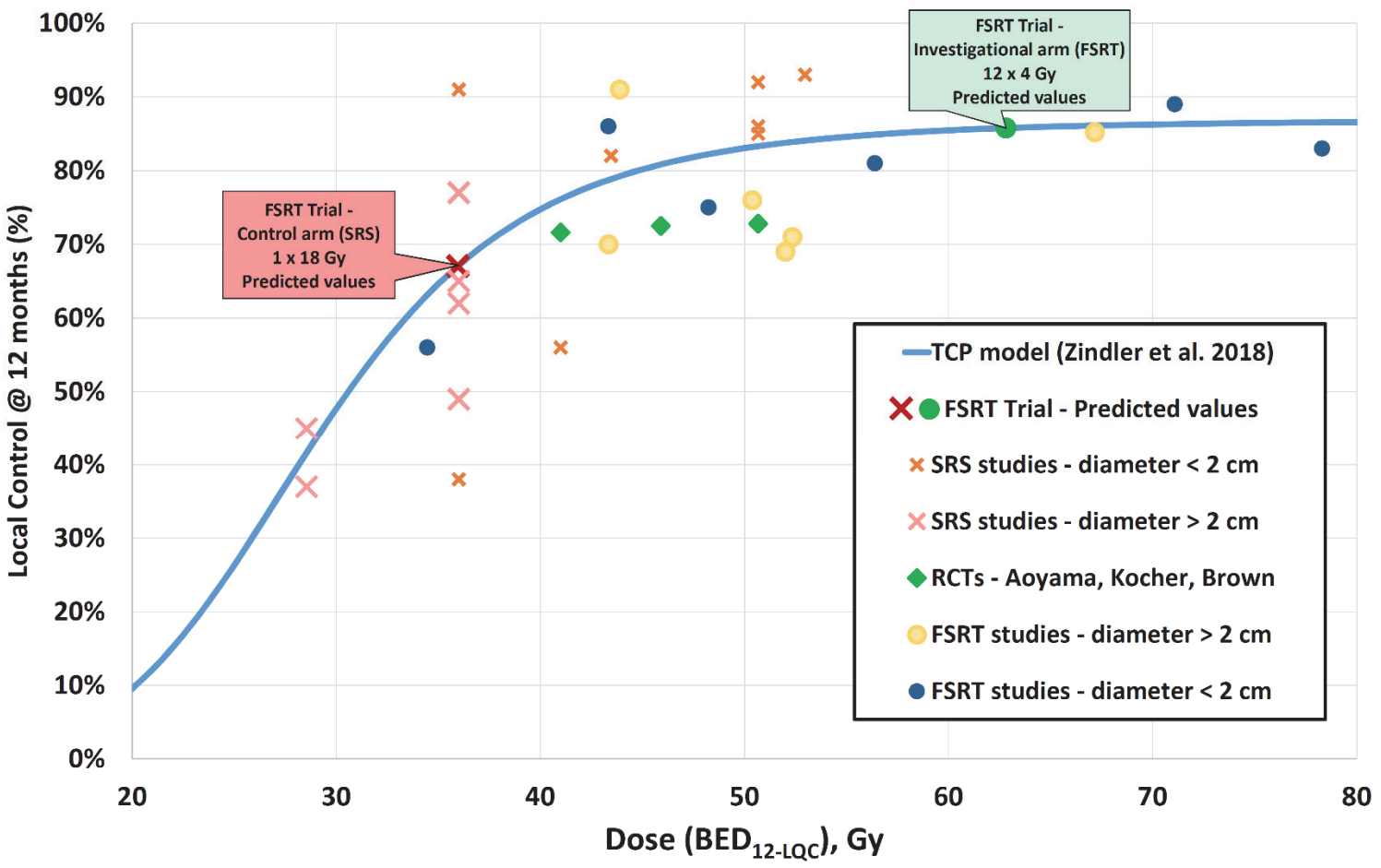


Figure 1 shows the relationship between the delivered $BED_{12\text{-}LQC}$ and local control at 12 months, as determined by Wiggenraad and Zindler (Wiggenraad et al. 2011, Zindler et al. 2018). The blue line represents the tumor control probability (TCP) model described by Zindler et al. This dose-response relationship has been derived from multiple studies for patients with brain metastases (see legend). The control arm will receive a $BED_{12\text{-}LQC}$ of 36 Gy in a single fraction of 18 Gy, and the experimental arm will receive a $BED_{12\text{-}LQC}$ of 62.8 Gy in multiple fractions (12 x 4 Gy fractionation scheme). Based on the established dose-response relationship, a local control rate of 67.1% in the control arm (red box) and 85.8% in the investigational arm (green box) could be expected. The figure has been adopted from Wiggenraad and Zindler but has been extended with the results of additional studies that have been published after the analysis by Wiggenraad et al. in 2011.

1.6. Study objectives

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 brain metastases between 1 - 4 cm 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 this 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. CNS side effects especially radiation necrosis will be evaluated as secondary objectives.

1.6.1. Primary objective

Improvement of local control in patients with large brain metastases treated with fractionated stereotactic radiotherapy (FSRT) versus single-fraction stereotactic radiosurgery (SRS) according to RTOG 9005 guidelines (gold standard)

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 (Lin et al. 2015). True local progression and radionecrosis are differentiated via a prespecified algorithm in the trial (see Section 8.3.).

If multiple metastases are treated in the trial, progression is defined as at least one metastasis fulfilling the criteria for progression.

1.6.2. 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 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.

Based on the *RANO-BM* criteria, progression is defined as an increase in volume of 72.8% or more (corresponds to a 20% increase in diameter for a perfect sphere). 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.

- Assessment of 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

1.6.3. Translational research projects

- Differentiation of radiation necrosis from recurrent tumor 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.

See also section 1.5.

2. Study design

2.1. Type of study

Investigator-initiated, multicenter, open, randomized controlled phase III superiority trial.

2.2. Sample size calculation

On the basis of available retrospective and dose-response relationship data, it is expected that SRS will result in a 12-month local tumor control rate of approximately 65% and that FSRT can increase this rate to about 80% (cf. Section 1.4.). This difference is considered to be clinically significant. A sample size of N=191 evaluable cases each in the experimental and control arm, respectively, corresponding to a total of 382 patients, is required to detect a significant difference i.e. an increase in TTLP at least this large at 12-month follow-up in a randomized comparison (see Section 10.2.). The number of TTLP events to be observed is 82.

2.3. Scope of the study

This is a multicenter study.

2.4. Time schedule

Start of study:	Q3 2020
Start of recruitment:	Q1 2021
Duration of recruitment:	3 Jahre
Duration of follow-up:	2 Jahre
End of study:	2026

Follow-up is performed for progression/radionecrosis as well as for overall survival, toxicity and distant progression, respectively. In case of local progression, radionecrosis or distant progression, follow-up for the other events as well as toxicities and overall-survival continues. In case of radionecrosis, follow-up for progression continues, if not determined by histology, as progression can occur after a lesion has experienced radionecrosis. Conversely, in case of progression, follow-up for radionecrosis for the respective lesion ends.

3. Selection of study population

3.1. Inclusion criteria

1. Age ≥ 18 years (no upper age limit)
2. Karnofsky Performance Scale (KPS) score >50
3. Life expectancy ≥ 3 months
4. 1 to 10 brain metastases from a solid tumor except small cell lung cancer and germinomas
5. 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)

6. Ability to understand the contents of the protocol and consent to participate, in writing
7. Written informed consent before enrollment in the study

3.2. Exclusion criteria

1. Whole-brain radiotherapy completed ≤ 6 weeks before study treatment or planned whole-brain radiotherapy following local radiotherapy
2. Prior radiotherapy of the metastasis or metastases to be irradiated in the present study
3. Relevant overlap of prior radiotherapy fields, cerebral or otherwise, with the metastasis or metastases to be irradiated in the present study
4. Location of metastasis to be irradiated in the brainstem.
5. Total of > 10 brain metastases, including previous metastases, at the time of inclusion in the study.
6. Cerebral metastases from small cell lung cancer or germinoma.
7. Contraindications to magnetic resonance imaging (e.g., metal implants, cardiac pacemaker, claustrophobia)
8. If a metastasis to be irradiated cannot be adequately differentiated in high-resolution, contrast-enhanced T1-weighted imaging for target volume delineation
9. Pregnant or nursing women
10. Women and men of reproductive age who are unwilling or unable to ensure highly effective contraceptive measures until 90 days following the last administration of radiation. (see 6.10 for details)
11. Chronic drug, medication or alcohol abuse
12. Psychological, familial, sociological, or geographical condition that would preclude study compliance
13. Nursing care patients
14. Inability to speak and understand German
15. Simultaneous participation in another clinical trial

4. Treatment plan

4.1. Indication for radiotherapy

The indication for radiotherapy will be determined according to the usual clinical standards or guidelines. The dose fractionation scheme, individual fraction size, total dose, and radiotherapy volume will be set in accordance with clinical standards and guidelines. The participating radiation oncologists will ensure each patient is able to receive radiotherapy according to protocol before he or she is included in the study.

4.2. Summary

Before the start of radiation treatment, each patient is randomly allocated to either fractionated stereotactic radiotherapy (FSRT = experimental arm) or to the "gold standard" treatment, single-fraction stereotactic radiosurgery according to RTOG 9005 (SRS = control arm). Randomization is stratified according to metastasis volume (< 14.1 cm^3, ≥ 14.1 cm^3) and primary tumor histology (radioresistant histology: melanoma, renal cell carcinoma and sarcoma vs. other).

Single fraction stereotactic radiosurgery (SRS = control arm) will be performed according to RTOG 9005 guidelines (gold standard) and delivered in a single fraction of 24 Gy (∅ 1-2 cm), 18 Gy (∅ 2-3 cm) or 15 Gy (∅ 3-4 cm), respectively, adjusted according to tumor diameter (∅). The dose is prescribed to the isodose line (50-80%) encompassing the metastasis with a safety margin of up to 1 mm depending on institution-specific accuracy.

Patients in the fractionated stereotactic radiotherapy group (experimental arm) will receive a total dose of 48 Gy in 12 daily fractions of 4 Gy each. An overall GTV-PTV safety margin of 2 mm will be used. The dose is prescribed to the 80% isodose line encompassing the PTV.

4.3. Randomization of subjects

Randomization is stratified according to metastasis volume (< 14.1 cm^3, ≥ 14.1 cm^3) and primary tumor histology (radioresistant histology: melanoma, renal cell carcinoma and sarcoma vs. other). If multiple cerebral metastases are treated in the trial, the total volume of all treated metastases is used for stratification.

Randomization will be performed on patient level.

4.4. Radiotherapy technique

4.4.1. Quality assurance for stereotactic radiotherapy

Participation requirements:

The following requirements are mandatory for all participating institutions and need to be achieved before the enrollment of patients at the respective site:

- Linear accelerator with ≥ 6 MV photons designed for stereotactic radiosurgery
- Patient immobilization: Individual patient immobilization with a dedicated thermoplastic mask system that is designed for stereotactic radiosurgery
- Image Guidance: A kV X-ray based imaging system using i) an on-board CT, ii) a supplementary in-room CT or iii) in-room X-ray is mandatory. An image-guidance system relying solely on surface tracking (e.g. Vision RT) is not acceptable.
- Collimation of irradiation: Multileaf collimator (MLC) with leaf width ≤ 5 mm centrally or cylindrical collimators of equivalent size (Schmitt et al. 2020).
- Mechanical accuracy: Spatial dose placement uncertainties need to be a maximum of 1 mm in system-specific end-to-end tests.
- Dosimetric accuracy: Point based plan-to-measurement differences must be ≤ 3% within the target using system-specific end-to-end or delivery-quality-assurance tests with homogeneous phantoms
- Dose calculation grid size: The dose calculation grid size has to be 2 mm or finer according to ICRU 91 (ICRU 2017).
- Dose calculation algorithm: Advanced type-b model-based dose calculation algorithms like Monte Carlo techniques and deterministic solvers (e.g. Acuros AXB, Varian) must be used (ICRU 2017).
- Dedicated quality assurance measures: Small field dosimetry for commissioning, system-specific end-to-end tests, the regular check of mechanical accuracy according to system specific instructions and daily quality control of the compliance of the image guidance system with the treatment isocenter are mandatory.
- The planning CT slice thickness should be ≤ 1.5 mm.
- MRI for target volume delineation, which must be performed no longer than 14 days before the start of RT of brain metastases in this study (Seymour et al. 2015).

- The MRI study used for target volume delineation must contain a high-resolution, contrast-enhanced T1-weighted series, for example T1-MP-RAGE, with a maximum slice thickness of 1 mm and isotropic resolution (see 7.1 for details).
- Distortions in the MRI for target volume definition must be minimized: **Vendor-specific 3D distortion correction** for gradient non-linearity-related distortions **is mandatory** and distortions due to magnetic field inhomogeneity should be minimized by patient-specific active shimming and appropriate pixel bandwidths. (Putz et al. 2020)
- Treatment planning system: A treatment planning system capable of stereotactic radiosurgery planning that allows for highly accurate rigid co-registration of planning CT and MRI images.
- Stereotactic radiotherapy may be delivered using coplanar and non-coplanar stereotactic arcs. Multiple isocenters and intensity modulated radiotherapy may be used to enable conformal dose delivery.
- Existing local expertise in treating patients with SRS or FSRT for brain metastases is required, i.e. at least 100 cranial SRS or FSRT treatments have been performed in the previous 3 years.

4.4.2. Patient positioning

Dedicated thermoplastic mask fixation systems designed for stereotactic radiosurgery will be used to position the patients for stereotactic radiotherapy and CT-based treatment planning in order to minimize positioning inaccuracy.

Image guidance is mandatory. A kV X-ray based imaging system using i) an on-board CT, ii) a supplementary in-room CT or iii) stereoscopic X-ray is required for patient positioning and after each couch rotation. An image-guidance system relying solely on surface tracking (e.g. Vision RT) is not acceptable.

Overall, a targeting accuracy of 1 mm or better should be achieved (Kocher et al. 2014).

4.4.3. Target volume delineation

The gross tumor volume (GTV) is defined as the demonstrable extent of the metastasis, as determined by high-resolution, contrast-enhanced T1-weighted magnetic resonance imaging with a maximum layer thickness of 1.5 mm performed no more than 14 days before the start of RT. Accurate GTV segmentation must be performed in each available layer at the voxel level.

Planning target volume definition varies according to treatment arm.

- Control arm – Single-session SRS according to RTOG 9005:

PTV = GTV + up to 1 mm margin depending on institution-specific accuracy

- Experimental arm - Fractionated stereotactic radiotherapy:
  PTV = GTV + 2 mm (i.e., the PTV corresponds to GTV with 2 mm isotropic expansion)

If isotropic expansion leads to overlapping with a critical organ at risk (OAR), such as the optic system, it is permissible to reduce the safety margin to 0 mm at the affected sites.

4.4.4. Definition of organs at risk (OAR)

Segmentation of the following organs at risk (OARs) must be performed during radiation planning: eyes (left & right), optic nerves (left & right), chiasma, pituitary gland, cochlea (left & right), and brain stem. Segmentation of the cervical spinal cord is also necessary in patients with very caudal lesions (cerebellum). In general, all OARs must be segmented completely along their entire extent (exception: spinal cord). The segmentation of optic nerves, chiasma, pituitary gland, cochlea and brainstem must be performed with the aid of the high-resolution MRI (layer thickness of the sequences used for segmentation must not exceed 1.5 mm).

4.4.5. Dose prescription and dose specification

Prescribing, recording and reporting should be performed according to the ICRU Report 91 guidelines. (ICRU 2017)

In the control arm, brain metastases will be treated by single-fraction SRS according to RTOG 9005 guidelines. These patients will receive a single fraction of either 24 Gy (diameter: ≥ 1 cm and < 2 cm), 18 Gy (diameter: ≥ 2 cm and < 3 cm) or 15 Gy (diameter: ≥ 3 cm and ≤ 4 cm), depending on the largest diameter of the metastasis to be irradiated.

Metastases in the experimental arm will be treated with hypofractionated stereotactic radiotherapy (FSRT). Patients in the FSRT group will receive a total dose of 48 Gy in 12 daily fractions of 4 Gy each (with weekend breaks).

The target-encompassing isodose should be 50-80% in the control arm (single-fraction SRS) and 80% in the experimental arm (FSRT).

The dose specification will be set to the target-encompassing isodose normalized to the maximum dose (Dmax = 100%). The dose calculation grid size has to be 2 mm or finer according to ICRU 91 (ICRU 2017). Advanced type-b model-based dose calculation algorithms like Monte Carlo techniques and deterministic solvers (e.g. Acuros AXB, Varian) must be used (ICRU 2017).

4.4.6. Radiotherapy plan quality requirements

The plan quality is assessed using the established metrics by Shaw et al. (Shaw et al. 1993) as well as by the new ICRU 91 guidelines (ICRU 2017).

The specified values have to be achieved.

Conformity Index:

The Conformity Index is defined as **$CI = V_{RI}/TV$**,
where V_{RI} is the volume of the encompassing prescription isodose
and TV is the volume of the planning target volume

Per Protocol: Conformity Index ≥ 1.0 and ≤ 2.0

Acceptable variation: Conformity Index ≥ 0.9 and < 1.0 OR > 2.0 and ≤ 2.5

Major deviation (Unacceptable): all other

Note: In the control arm (SRS), if normal brain tissue constraints can't be met otherwise, the lower boundary for per protocol is decreased to 0.9 and the lower boundary for acceptable variation is lowered to 0.8 (see below).

Coverage:

The Coverage is defined as **$Q = I_{min}/I_{pre}$**,
where I_{min} is the minimum dose, the target receives
and I_{pre} is the prescribed dose.

Per Protocol: Coverage ≥ 0.9

Acceptable variation: Coverage 0.8 – 0.9

Major deviation (Unacceptable): all other

Note: In the control arm (SRS), if normal brain tissue constraints can't be met otherwise, the lower boundary for per protocol is decreased to 0.8 and the lower boundary for acceptable variation is lowered to 0.7 (see below).

Homogeneity Index:

The Homogeneity Index is defined as **$HI = I_{max}/I_{pre}$**,
where I_{max} is the maximum dose, the target receives
and I_{pre} is the prescribed dose.

Per Protocol: Homogeneity Index ≤ 2

Acceptable variation: Homogeneity Index > 2.0 and ≤ 2.5

Major deviation (Unacceptable): all other

4.4.7. Simulation and documentation

Isodose distributions, dose-volume histograms (DVHs) for organs at risk and target volumes (GTV, PTV) are mandatory for radiation planning and must be documented. Image-guided radiotherapy (IGRT) with daily position

verification is also mandatory. All radiation treatment records must be kept on file for 30 years, pursuant to Article §85 (3) of the German Ordinance on the Protection against Damage and Injuries Caused by Ionizing Radiation (Radiation Protection Ordinance, StrlSchV). Prescribing, recording and reporting should be performed according to the ICRU Report 91 guidelines. (ICRU 2017)

4.4.8. Radiotherapy plan quality assurance review

All radiotherapy treatment plans are to be submitted electronically using the eCRF system in the DICOM-RT format to enable analysis of radiotherapy treatment plan quality including planning CT and MRI, DICOM structures and dose distribution. Analysis of radiotherapy treatment quality will be conducted by random sampling and institutions will receive feedback based on the conducted analyses. A systematic analysis of radiotherapy treatment quality will be performed after completion of accrual. Upload of the radiotherapy treatment plan must be completed withing 4 weeks of treatment delivery.

4.4.9. Normal tissue constraints

The dose limits that must not be exceeded for organs at risk are listed in the table below.

Organs at Risk	**Maximum Dose**	
	SRS (control arm)	**FSRT (investigational arm)**
Optic nerves	8,0 Gy	32 Gy
Chiasma	8,0 Gy	32 Gy
Eyes (retina)	8,0 Gy	32 Gy
Brainstem	12,0 Gy	36 Gy
Pituitary gland	15,0 Gy	36 Gy
Cochlea	3,7 Gy (Mean Dose)	32 Gy
Brain tissue	See Section 4.4.10. below	

Reduction of margin:

If the planned isotropic expansion leads to overlapping with a critical organ at risk (OAR), such as the optic system, it is permissible to reduce the safety margin to 0 mm at the affected sites in both the SRS and FSRT arm.

4.4.10. Sparing of healthy brain tissue

As a basic principle, healthy brain tissue should be treated as sparingly as possible without compromising the radiation dose prescribed to the tumor.

Control arm (SRS):

V_{10Gy} and V_{12Gy} are well-described predictors for the occurrence of radionecrosis associated with the use of single-fraction SRS according to RTOG 9005 for brain metastases (Blonigen et al. 2010):

	SRS (control arm)
Normal brain	$V_{10Gy} \leq 10.5$ cm³ $V_{12Gy} \leq 7.9$ cm³

A $V_{10Gy} \leq 10.5$ cm³ and a $V_{12Gy} \leq 7.9$ cm³ are reference values in the trial, however, frequently can't be achieved with large metastases (Kirkpatrick et al. 2015, Minniti et al. 2016). Instead V_{10Gy} and V_{12Gy} should be minimized as far as reasonably possible as judged by the treating physician.

The following options are available in the trial, if V_{10} and V_{12} need to be further reduced at the discretion of the treating physician and other aspects of treatment planning have already been fully optimized:

- The required lower boundary for the Conformity Index is decreased to 0.9. The lower boundary for an acceptable variation for Conformity Index is reduced to 0.8.
  In addition, regarding Coverage the lower boundary for per protocol is decreased to 0.8 and the lower boundary for acceptable variation is lowered to 0.7.
- It is permitted to reduce the prescription dose down to 23 - 18 Gy (diameter: ≥ 1 cm and < 2 cm), 17 - 15 Gy (diameter: ≥ 2 cm and < 3 cm) or 14 - 12 Gy (diameter: ≥ 3 cm and ≤ 4 cm) which constituted the previous dose steps for metastases treated in the RTOG 9005 trial.
- Contact the Study coordination office (Tel. 09131 85-33968)

Investigational arm (FSRT):

Maximal sparing of healthy brain tissue is also pursued in the experimental arm. The dose prescription specified in the study protocol should not be compromised, however.

4.5. Side effects of radiotherapy

Any of the general side effects of radiotherapy in the neurocranial area may, in principle, occur (see, for example, proCompliance, Documented Patient Information, Radiosurgery and Stereotactic Radiosurgery):

Common:	Edema (swelling from the accumulation of fluid in the brain), which can trigger or aggravate disease-related complaints such as paralysis, seizures and headaches Localized brain tissue death (brain necrosis), which in rare cases may be associated with neurological deficits (e.g., paralysis) Damage to healthy nerve cells cannot be ruled out with certainty and may result in temporary or, in rare cases, permanent paralysis (e.g., of the extremities or facial nerves) or loss of senses (e.g. deterioration or loss of vision, hearing loss)
Rare:	Hair loss in the irradiated area Hemorrhage in irradiated metastases
Very rare:	Wound healing disorders in the irradiated area after later surgery or injury Impairment of concentration and memory Dryness, slight redness and inflammation of the skin very rarely occur after stereotactic radiosurgery

Possible late complications of radiotherapy:

Common:	Localized brain tissue death (brain necrosis) with swelling of the surrounding tissues, which in rare cases may be associated with neurological deficits (e.g., paralysis)
Rare:	Permanent hair loss at the irradiated site Sensitivity to weather in association with headaches Rapid fatigue with increased need for sleep, reduction of mental speed; permanent reduction of concentration and memory Reduced hormone production in the diencephalon and pituitary gland (hypophysis); the resulting hormone deficits affect the metabolism and sexuality but can be compensated by hormone replacement therapy
Very rare:	Deterioration of hearing or vision Optic nerve damage, which may result in blindness Radiotherapy slightly increases the natural risk of developing a second tumor in later years. This is particularly true when combined with cytostatic chemotherapy.

4.6. Modification of the radiotherapy regimen

In principle, the study protocol does not provide for the interruption or even discontinuation of the specified radiotherapy regimen. This is only possible at the discretion of the responsible radio-oncologist if there is good reason for doing so. Likewise, the individual reference dose, total reference dose and PTV can be modified in such an event at the discretion of the radio-oncologist. The radio-oncologist must make such a decision on an individual patient basis and inform the study center of the decision. (see also the

sections: 4.4.3. Target volume delineation, 4.4.9. Normal Tissue Constraints as well as 4.4.10. Sparing of healthy brain tissue)

4.7. Systemic treatment during and in close temporal relationship to radiotherapy

Certain systemic treatments may increase the risk for side effects when administered concurrently with stereotactic radiotherapy for cerebral metastases. The following guidelines have been defined in this trial to assure a safe and standardized practice regarding systemic treatment during radiotherapy.
In addition to concurrent treatment, some high-risk systemic agents, such as BRAF-inhibitors, may also increase the risk for CNS side effects, when they are administered in close temporal relationship to stereotactic radiotherapy (see Section 4.7.1. "Additional safeguards with respect to high-risk systemic agents" below).

Control arm (SRS):

Concurrent systemic treatment should not be administered on the days, on which single-session radiosurgery (SRS) is given.

Please also notice the additional safeguards for high-risk systemic agents described below.

Investigational arm (FSRT):

Due to the prolonged treatment delivery in fractionated stereotactic radiotherapy (FSRT) certain systemic agents may be administered during radiotherapy. Table 3 and 4 provide a list of systemic treatments that may be administered during FSRT and those that must not be given during treatment.

Please also notice the additional safeguards for high-risk systemic agents described below.

Table 3: Systemic agents that may be administered during FSRT

Systemic agent	Source
Anti-PD-1 / Anti-PD-L1 antibodies *may be given during FSRT*	(Chen et al. 2018)
Bevacizumab *may be given during FSRT*	(Levy et al. 2014)
Capecitabine, 5-Fluorouracil *may be given during FSRT*	(Chargari et al. 2009)
Cetuximab *may be given during FSRT*	No reports of increased toxicity were identified
Cisplatin, Carboplatin *may be given during FSRT*	(Verduin et al. 2017)
Crizotinib, ceritinib, alectinib *may be given during FSRT*	No conclusive evidence of increased toxicity was identified (Kroeze et al. 2017)
Etoposide *may be given during FSRT*	(Chen et al. 2012)
Gefitinib/Erlotinib *may be given during FSRT*	(Kroeze et al. 2017)
Ifosfamide *may be given during FSRT*	(Quantin et al. 1999)
Ipilimumab *may be given during FSRT*	(Mathew et al. 2013, Kiess et al. 2015, Chen et al. 2018)
Lapatinib *may be given during FSRT*	(Yomo et al. 2013)
Mitomycin *may be given during FSRT*	(Furuse et al. 1997)
Paclitaxel, Docetaxel *may be given during FSRT*	(Arrieta et al. 2011)
Pemetrexed *may be given during FSRT*	(Dinglin et al. 2013)
Sorafenib/Sunitinib *may be given during FSRT*	(Kroeze et al. 2017)
Trastuzumab *may be given during FSRT*	(Chargari et al. 2011)
Vindesine *may be given during FSRT*	(Furuse et al. 1997)
Vinorelbine *may be given during FSRT*	(Quantin et al. 1999)

Table 4: Systemic agents that must not be administered during FSRT

Systemic agent	Source
BRAF Inhibitors (e.g. vemurafenib, dabrafenib) must *not* *be given during FSRT*	(Anker et al. 2016)
Gemcitabine must *not* *be given during FSRT*	(Huang et al. 2007)
MEK Inhibitors (e.g. trametinib and cobimetinib) must *not* *be given during FSRT*	(Anker et al. 2016)
Trastuzumab emtansine (T-DM1) must *not* *be given during FSRT*	(Carlson et al. 2014, Mitsuya et al. 2016, Geraud et al. 2017)

For agents not yet listed above please contact the Study coordination office (Tel. 09131 85-33968).

4.7.1. Additional safeguards with respect to high-risk systemic agents

BRAF- and MEK-Inhibitors:

BRAF- as well as MEK-Inhibitors (such as dabrafenib and vemurafenib as well as trametinib and cobimetinib) must not be administered ≥ 3 days before and after radiotherapy in both treatment arms (Anker et al. 2016).

Gemcitabine:

Gemcitabine must not be administered ≥ 7 days before and after radiotherapy in both treatment arms.

Trastuzumab emtansine (T-DM1):

Due to multiple reports of increased risk for radionecrosis T-DM1 must not be administered ≥ 20 days before and after radiotherapy in both treatment arms, which corresponds to 5 times the half-life (Carlson et al. 2014, Geraud et al. 2017).

5. Clinical examinations and status assessments

5.1. Schedule of examinations and procedures

5.1.1. Screening examinations before treatment

1. **Magnetic resonance imaging (MRI) of the brain**
   Note: Time from MRI to start of radiotherapy has to be ≤ 14 days
2. **Performance status assessment**
   ECOG / KPS
3. **Assessment of Adverse Events before treatment (Medical history relevant for the study)**
   NCI CTCAE v5.0
4. **Assessment of Quality of Life**
   EORTC QLQ-C30
   EORTC QLQ-BN20
5. **Assessment of RPA and GPA prognostic scores**
6. **Documentation of glucocorticoid dose**
7. **Documentation of systemic treatment including prior systemic therapies**
8. **Written informed consent**
9. **Pregnancy test in women of childbearing potential**
   Pregnancy should be ruled out by determining Serum β-HCG
10. **Planning CT**

5.1.2. Examinations immediately after radiotherapy

A deviation from the last day of radiotherapy up to ± 2 days due to organizational reasons is acceptable. With SRS the examination has to take place after the treatment was administered, however.

1. **Performance status assessment**
   ECOG / KPS
2. **Assessment of Adverse Events**
   NCI CTCAE v5.0
3. **Assessment of Quality of Life**
   EORTC QLQ-C30
   EORTC QLQ-BN20
4. **Documentation of glucocorticoid dose**
5. **Documentation of systemic treatment**

5.1.3. Final examination

6 weeks after the last radiation treatment. A deviation from the exactly specified date of up to ± 1 week is acceptable. 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.

1. **Magnetic resonance imaging (MRI) of the brain**

2. **Performance status assessment**
   ECOG / KPS
3. **Assessment of Adverse Events**
   NCI CTCAE v5.0
4. **Assessment of Quality of Life**
   EORTC QLQ-C30
   EORTC QLQ-BN20
5. **Documentation of glucocorticoid dose**
6. **Documentation of systemic treatment**

5.1.4. Follow-up examinations

3 months after radiotherapy, then every 3 months up to a period of 2 years after the last radiation treatment. A deviation from the exactly specified date of up to ± 2 week is acceptable. 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.

1. **Magnetic resonance imaging (MRI) of the brain**
2. **Performance status assessment**
   ECOG / KPS
3. **Assessment of Adverse Events**
   NCI CTCAE v5.0
4. **Assessment of Quality of Life**
   EORTC QLQ-C30
   EORTC QLQ-BN20
5. **Documentation of glucocorticoid dose**
6. **Documentation of systemic treatment**

5.2. General health status assessment

The KPS Index and ECOG Performance Status will be used to assess each patient's general health status. (Table 5)

Table 5: Performance Scales

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	0	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
Care for self. Unable to carry on normal activity or to do active work	70	1	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent	50	2	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalization indicated	30	3	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5.3. Recording of adverse events

The Common Terminology Criteria for Adverse Events for Adverse Events (CTCAE) Version 5.0 established by the National Cancer Institute (NCI) will be used for the documentation of adverse events (AEs). AEs will be recorded before radiotherapy, after the last radiation treatment, 6 weeks after the end of radiotherapy, 3 months after the end of radiotherapy, and then every 3 months for a follow-up period of 2 years.

For information on adverse event reporting according to CTCAE, see https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

5.4. FSRT Trial examination schedule

The FSRT Trial examination schedule is depicted at page 5.

6. Ethical and legal requirements

6.1. Ethics review

This study will not be started before review and approval by the responsible ethics committees has been obtained.

6.2. Ethical conduct of the study

This study protocol (and any future amendments to it) is drafted (will be drafted) in accordance with the ethical principles in the current version of the Declaration of Helsinki (see https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/).

The study has been registered at ClinicalTrials.gov (www.clinicaltrials.gov NCT03697343) and at the German Clinical Trials Register (www.drks.de - DRKS00015647).

6.3. Informed consent

Before recruitment into the clinical trial each patient will be informed, that participation in the study is completely voluntary, and that he or she may withdraw the participation in the trial at any time without any declaration of reasons. This will not lead to any disadvantage for the respective patient. If the withdrawal is caused by any adverse events, the patient should inform the investigator about this fact. The investigator will inform the patient about the treatments to be used and their possible adverse effects. At the same time, he/she will be informed on the nature and objectives of the study, expected advantages of the participation, possible hazards of the study and alternatives of treatment. The patient will have sufficient time for his decision and opportunity to ask additional questions. Moreover, the patient will receive a written "Patienteninformation" (see Appendix), containing all relevant information for the patient's decision and the course of the study. The consent of the patient to participate must be obtained in writing before recruitment into the study. The informed consent form "Einwilligungserklärung" (see Appendix) must be dated and signed by the patient. Thereby, he declares his voluntary consent to participate in the study and his willingness to comply with the requirements of the trial and the instructions of the treating investigator during the course of the study. He also agrees that data on his disease are recorded within the framework of the clinical trial and that they are transferred in a pseudonymized way. Moreover, the patient agrees that delegates from the responsible authorities or the study management may have direct access to his/her original medical records for trial related monitoring, audit, review and regulatory inspection. The original informed consent form has to be stored in the Investigator Site

File. The patient receives a copy and one copy is filed in the patient's hospital documents. First, the patient has to date and sign the informed consent form. The investigator obtaining the informed consent has to date and sign the informed consent form after the patient. The informed consent is only valid after receiving the patient's signature.
The Patient Information Sheet, Informed Consent Form and all other documents to be issued to study participants will be submitted to the responsible ethics committee for approval prior to their use.

6.4. Subject data protection

Regulations of the data protection legislation are followed. It is assured that clinical and demographic data about study patients is always submitted and stored in a pseudonymized manner. Each study patient is identified by a pseudonym. Study patients must be informed about the transfer of their pseudonymized data. The identifying personal information about a patient is retained at the Trial office. Only the investigator or administrative staff is able to reveal a pseudonym. In accordance to the guidelines of the Ethics Committees initials are considered as personal information, are never transmitted and remain at the medical site. Persons that do not consent to transfer of their pseudonymized data will not be included in the study.

6.5. Audits and inspections

In case of an audit by the study management or an appropriate authority the investigator will make available all relevant documents. If an audit visit by a regional authority is announced, the respective center should inform the coordinating investigator as early as possible to allow for an appropriate preparation and support. The inspected investigator or organizational institution of the study will be informed on the result of the audit.

Internal quality reviews will take place at the meetings of the study participants. Therefore, the reference board will instruct the participating centers to present their primary documentation of study procedures. The results will be discussed at the meetings to improve the quality of procedures and documentation.

6.6. Documentation

All the data retrieved during the conduct of the study are entered into the appropriate electronic case record forms (eCRF) by the investigator or another person authorized by the investigator in a timely manner.

6.7. Data Management

The Medical Center for Information and Communication Technology (MIK) and the Winicker Norimed GmbH will develop and validate the study database according to its Standard Operating Procedures prior to the start of data entry. The data management system is based on commercial

research software that stores the data in a database. All changes made to the data are stored in an audit trail. The study software has a user and role concept that can be adapted to the specific needs of the study. The database is integrated into a general IT infrastructure and security concept that has a firewall and a backup system. Daily backups of the data will be performed. After data completion and cleansing, the database will be closed and the data exported for statistical analysis.

6.8. Data storage

All relevant study documents including the eCRFs are stored at the office of the coordinating investigator/sponsor for 30 years in accordance with the German X-ray Ordinance (RöV) or Radiation Protection Ordinance (StrlSchV). The investigators have to archive major administrative documents (correspondence with ethical committee, authorities, sponsor etc.), the patient identification log, the signed informed consent forms, and the main study documents (protocol, amendments) for the same time period. The original patient records have to be archived according to the standard procedures of the respective institution, but at least for 30 years. The patient identification list will be stored separate from the documentation records.

6.9. Handling and documentation of pregnancies

Pregnant and breastfeeding women are generally excluded from participating in this study. If a female patient or the female partner of a male patient should become pregnant during the treatment period or within 6 months after the last study treatment, the responsible investigator must document this in the patient records and inform the principal investigator accordingly. Pregnant study participants must end their participation in the clinical trial immediately. The pregnancy must be monitored and documented throughout the full course of pregnancy and up to 8 weeks after birth. The attending gynecologist may be consulted, as needed; the participant's consent is required for this.

6.10. Contraception

For this trial, male subjects will be considered to be of non-reproductive potential if they are permanently sterile by bilateral orchidectomy.

Female subjects will be considered of non-reproductive potential if they are either:

- postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In

the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.)
- have had a hysterectomy and/ or bilateral oophorectomy and/ or bilateral salpingectomy, at least 6 weeks prior to screening.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, from screening to 90 days after the last administration of radiotherapy by complying with one of the following:

1) practice abstinence* from heterosexual activity

OR

2) use of highly effective contraception during heterosexual activity by both themselves and their partners with reproductive potential.

*Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

Methods of contraception for females with childbearing potential must be highly effective. The following methods are allowed:

1) combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
   - oral
   - intravaginal
   - transdermal
2) progestogen-only hormonal contraception associated with inhibition of ovulation:
   - oral
   - injectable
   - implantable
3) intrauterine device (IUD)
4) intrauterine hormone-releasing system (IUS)
5) bilateral tubal occlusion

Required highly-effective contraception methods for men are:

1) Bilateral vasectomy (after medical assessment of surgical success)
2) Condoms + spermicidal agent

6.11. Withdrawal by the subject

Subjects are free to withdraw from the study at any time with or without explaining the reason(s) for withdrawal and without incurring any disadvantages from withdrawal. The responsible investigator must document the date of withdrawal, the data collected up until the point of withdrawal, and the reason(s) for withdrawal, if known. In a patient wishes to withdraw from study, the investigator should perform all examinations

normally conducted during the final study visit at the time of the last follow-up visit.

6.12. Withdrawal by the responsible study physician

Subjects must be withdrawn from the study in the event of:

- Adverse events that do not permit further treatment or which make further study participation seem unadvisable due to the low information value of the data collected
- Circumstances that make it impossible to adhere to schedule of examination visits specified in the study protocol
- Lack of adequate patient compliance.

7. Assessment of Efficacy

7.1. Magnetic resonance imaging protocol

The magnetic resonance imaging (MRI) protocol used for treatment planning and during imaging follow-up should generally follow the recommendations of the brain tumor imaging protocol for clinical trials in brain metastases (BTIP-BM) (Kaufmann et al. 2020).

In addition to the BTIP-BM recommendations, **vendor-specific 3D distortion correction for gradient non-linearity-related distortions is mandatory** and distortions due to magnetic field inhomogeneity should be minimized by patient-specific active shimming and appropriate pixel bandwidths. Distortion correction is required for both precise radiotherapy treatment delivery and exact response and progression assessment during imaging follow-up.

7.2. Principles of Assessment

Differentiation between radionecrosis and local progression:

Following stereotactic radiotherapy, it can be difficult to differentiate true tumor progression from radiation necrosis (Chao et al. 2013, Lin et al. 2015, Soffietti et al. 2017). Frequently, a definitive differentiation is only possible with longer imaging follow-up or histologic diagnosis. Due to the large initial size of metastases included in this trial, surgical resection, if possible, constitutes the best diagnostic and therapeutic approach in the case of sustained or symptomatic enlargement and is therefore generally encouraged. As recommended in the *RANO-BM* guidelines, an algorithm (see Section 8.3.) is prespecified in the FSRT Trial to provide differentiation between radionecrosis and progression and enable standardized management in the case of an enlarging lesion.

Criteria used for assessment:

The *RANO-BM* criteria are used in the FSRT Trial for the definition of progression (Lin et al. 2015). As the assessment of local control is the primary aim of the FSRT Trial, only lesions treated as part of the trial are used for the definition of progression in accordance with the *RANO-BM* guidelines for localized therapy trials. For the same reason, corticosteroid use, and clinical status are not used for the definition of local control in this trial.

Assessment if multiple brain metastases are treated in the FSRT Trial:

If multiple brain metastases are treated in the FSRT Trial, local control or radionecrosis will first be determined for each metastasis treated in the trial according to the criteria described in 7.3. and the algorithm for the differentiation between radionecrosis and progression provided in 7.4. If at least one metastasis fulfills the criteria for progression or radionecrosis, this is scored as an event, i.e. as progression or radionecrosis event on a patient

level. If at least one metastasis fulfills the criteria for progression and at least one fulfills the criteria for radionecrosis, this is scored as both a progression and a radionecrosis event on a patient level. This definition is used as it is better suited for the assessment of efficacy and tolerability of multiple local treatments than a combined metric.

7.3. Methods and criteria for efficacy evaluation

Imaging studies for the determination of tumor control will be performed as specified in the Examination Schedule. In addition to MRI-based radiotherapy planning, MRI studies will first be performed 6 weeks after the last RT treatment and then every 3 months thereafter in accordance with the general guidelines for routine diagnostic imaging in the absence of progression or clinical symptoms. Imaging intervals may need to be shortened, if an increase in size has occurred (see below). If the patient develops any signs or symptoms suspicious of progression or radionecrosis an MRI should be performed promptly.

Primary endpoint: Local control and radionecrosis according to unidimensional criteria

Local progression is 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.

If a metastasis has fulfilled these criteria for progression but shows spontaneous regression during subsequent imaging follow-up back to baseline or nadir diameter or a relative decrease in the longest diameter of at least 30% compared to the maximum size during enlargement, this will be scored as radionecrosis instead of progression (see 8.3). A decrease in diameter of at least 30% corresponds to the *RANO-BM* criteria for partial response in brain metastases. The date of the event will be backdated to the first imaging showing an increase in largest diameter of at least 20% and 5 mm or more. Similarly, if a metastasis shows regression according to the above-mentioned criteria after initiation of treatment for suspected radionecrosis (e.g. corticosteroids, Bevacizumab), this will also be scored as radionecrosis.

It is possible for a lesion to experience radionecrosis first, e.g. a transient increase in diameter followed by a spontaneous regression according to the above-mentioned criteria, and true progression, e.g. an increase in diameter without spontaneous regression, during subsequent follow-up.

If a tissue sample is obtained from a metastasis treated as part of the trial, the histology will be classified as “radionecrosis”, “viable tumor” or “both” as has been done in the RTOG 9005 trial (Shaw et al. 2000). If the histology shows radionecrosis or viable tumor, this will be scored as radionecrosis or progression, respectively independent from any imaging metrics. In the case of radionecrosis, this will be scored as radionecrosis event, in the case of

viable tumor, this will be scored as progression event and in the case of viable tumor and radionecrosis, this will be scored as both radionecrosis and progression event. The time of the respective event will be backdated to the first imaging showing an increase in largest diameter of at least 20% and 5 mm or more. If no increase in size has occurred, the date of the procedure will be the date of the event.

If multiple brain metastases are treated as part of this trial, local progression is defined as at least one metastasis fulfilling the criteria for progression and radionecrosis is defined as at least one metastasis fulfilling the criteria for radionecrosis.

Secondary endpoint: Local control and radionecrosis according to volumetric criteria

Progression will be defined as a 72.8% increase in tumor volume, corresponding to a 20% increase in diameter of a perfect sphere, using volumetric criteria derived from the *RANO-BM* criteria.

If a metastasis has fulfilled these criteria for progression but shows spontaneous regression during subsequent imaging follow-up back to baseline or nadir volume or a relative decrease in tumor volume of at least 65.7% compared to the maximum volume during enlargement, this will be scored as radionecrosis instead of progression (see 8.3.). A relative decrease in metastasis volume of 65.7% corresponds to a 30% decrease in diameter of a perfect sphere and conforms with the criteria for partial volumetric response proposed by the *RANO-BM* working group. The date of the event will be backdated to the first imaging showing an increase in tumor volume of at least 72.8%. Similarly, if a metastasis shows regression according to the above-mentioned criteria after initiation of treatment for suspected radionecrosis (e.g. corticosteroids, Bevacizumab), this will also be scored as radionecrosis.

It is possible for a lesion to experience radionecrosis first, e.g. a transient increase in volume of 72.8% or more followed by a spontaneous regression, and true progression, e.g. an increase in volume without spontaneous regression, during subsequent follow-up.

If a tissue sample is obtained from a metastasis treated as part of the trial, the histology will be classified as “radionecrosis”, “viable tumor” or “both” as has been done in the RTOG 9005 trial (Shaw et al. 2000). If the histology shows radionecrosis or viable tumor, this will be scored as radionecrosis or progression, respectively independent from any imaging metrics. In the case of radionecrosis, this will be scored as radionecrosis event, in the case of viable tumor, this will be scored as progression event and in the case of viable tumor and radionecrosis, this will be scored as both radionecrosis and progression event. The time of the respective event will be backdated to the first imaging showing an increase in tumor volume of at least 72.8%. If no increase in size has occurred, the date of the procedure will be the date of the event.

If multiple brain metastases are treated as part of this trial, local progression is defined as at least one metastasis fulfilling the criteria for progression and radionecrosis is defined as at least one metastasis fulfilling the criteria for radionecrosis.

Distant brain failure:

Distant brain failure is defined in accordance with the *RANO-BM* guidelines as the appearance of new or progressive lesions distant from the metastases treated as part of the trial.

Distant lesions will be defined as having no direct contact to the initial volume of the metastases treated in the trial as determined by rigid coregistration of the baseline MRI to the follow-up MRI during central review.

Cause of death:

Cause of death will be determined for brain-metastasis specific survival as "death associated with brain metastases" and "death not associated with brain metastases". Mandatory criteria for death associated with brain metastases are progressive neurologic dysfunction and local progression as per the criteria described above or progressive neurologic dysfunction and distant brain failure.

Additional Assessments:

The following assessments, examinations and questionnaires will be completed at all visits: The ECOG Performance Status will be used to assess the patient's general health. Adverse events and toxicities identified by querying the patient will be documented based on the Common Terminology Criteria for Adverse Events (NCI CTCAE Version 5.0). The patient's quality of life will be assessed using the EORTC QLQ-C30 and EORTC QLQ-BN20 quality of life questionnaires. Corticosteroid use and current systemic therapies will be documented.

7.4. Algorithm in the case of an enlarging lesion

As soon as a lesion treated in the trial shows an increase in maximum diameter of at least 20 % and 5 mm or more compared to baseline or nadir diameter during central review of imaging data, this is preliminary scored as progression and the patient enters this algorithm. The aim of this algorithm is to provide definitive differentiation between radionecrosis and progression and to enable standardized management in the case of an enlarging lesion.

Glucocorticoid-resistant symptoms:

If the patient shows neurologic symptoms that are resistant to glucocorticoid treatment or if the patient is symptomatic and glucocorticoid treatment is contraindicated, resection of the enlarging lesion is advised. Resection will provide definitive histologic diagnosis. Histology will be classified as "radionecrosis", "viable tumor" or "both" as has been done in the RTOG 9005 trial (Shaw et al. 2000). In the case of radionecrosis, this will be scored as radionecrosis event, in the case of viable tumor, this will be scored as progression event and in the case of viable tumor and radionecrosis, this will be scored as both radionecrosis and progression event. The time of the respective event will be backdated to the first imaging showing an increase in largest diameter of at least 20% and 5 mm or more. If resection is not possible or if the patient denies surgery, stereotactic biopsy is recommended. Scoring will be performed as mentioned for resection. If stereotactic biopsy is not possible, an amino acid or FDG-PET coregistered to MRI is recommended. In the case of findings suggestive of radionecrosis on amino acid or FDG-PET a trial with Bevacizumab is advised according to Levin et al (Levin et al. 2011, Chao et al. 2013, Soffietti et al. 2017). Imaging intervals should be shortened to 6 weeks or less. If the metastasis shows regression after initiation of bevacizumab or corticosteroids or regresses spontaneously during subsequent imaging follow-up back to baseline or nadir diameter or shows a relative decrease in the longest diameter of at least 30% compared to the maximum size during enlargement, this will be scored as radionecrosis instead of progression. Else if the lesion receives additional treatment, i.e. Whole brain radiotherapy, repeat stereotactic radiotherapy or systemic treatment with established CNS effect, if the patient dies or is lost to follow-up or if routine study follow-up ends, this is scored as progression and the time of the event will be backdated to the first imaging showing an increase in largest diameter of at least 20% and 5 mm or more.

No Glucocorticoid-resistant symptoms:

In the absence of glucocorticoid-resistant symptoms, a trial with dexamethasone in a total dose of 4 – 24 mg daily depending on comorbidities and prior steroid dose is recommended. If contraindications to steroid treatment exist or if the patient is asymptomatic, imaging follow-up without initiation of steroids is possible. Imaging intervals will be shortened to 6 weeks. In the case of progressive symptoms an MRI has to be performed promptly. If short-term follow-up imaging or any subsequent imaging shows an increase in metastasis diameter of additional 20% and 5 mm or more compared to the first imaging showing the initial increase of at least 20% and 5 mm or more in diameter, it is advised to proceed as described under Glucocorticoid-resistant symptoms. Otherwise MRI follow-up will continue at 6-weeks interval. If the metastasis diameter decreases again to baseline or nadir levels or if the metastasis diameter decreases by at least 30% compared to the maximum diameter during enlargement, this is scored as radionecrosis event and the patient continues with routine study follow-up. The time of the event will be backdated to the first imaging showing an increase in largest diameter of at least 20% and 5 mm or more.

Else if the lesion receives additional treatment, i.e. Whole brain radiotherapy, repeat stereotactic radiotherapy or systemic treatment with established CNS effect, if the patient dies or is lost to follow-up or if routine study follow-up ends, this is scored as progression and the time of the event will be backdated to the first imaging showing an increase in largest diameter of at least 20% and 5 mm or more.

If it is clinically determined necessary by the treating physician deviation from the above-mentioned algorithm is possible after consultation with the Principal Investigator.

7.5. Central review of imaging data

Progression status will be assessed by a blinded central independent review at the neuroradiological reference center.

All imaging data must be uploaded into the provided eCRF system within 7 days.

7.6. Methodological continuity

All tests and examinations will be carried out under identical conditions, at the time points specified in the Examination Schedule.

8. Assessment of Safety

8.1. Assessment and reporting of adverse events

8.1.1. Terminology

Adverse Events are diseases, signs or symptoms, that occur or worsen after initiation of study treatment.

8.1.2. Assessment criteria

The severity of adverse events will be graded as per the assessment criteria of NCI CTCAE Version 5.0:

- Grade 1 (mild)
- Grade 2 (moderate)
- Grade 3 (severe)
- Grade 4 (life-threatening)
- Grade 5 (fatal)

If the severity of an AE should change during the observation period, the highest severity of the AE will be recorded.

The investigator must assess the causality of each adverse event. Causal relationships can be defined as follows:

- Causal relationship with the tumor
- Causal relationship with radiation treatment
- Causal relationship with other treatment measures
- Other
- Unknown

8.1.3. Documentation of adverse events

All Adverse Events must be documented according to NCI CTCAE v5.0 with its highest NCI CTCAE severity grade in the appropriate toxicity section of the eCRF, together with a short judgment on causality.

The following information must be recorded for each adverse event:

- Description of the Adverse Event according to CTCAE v5.0
- Date of onset and date of resolution
- The grade as assessed by the investigator according to the definitions in NCI-CTCAE 5.0
- Assessment of causality
- Outcome
- Treatment or action taken
- Led to study discontinuation: Yes/No

It is the responsibility of the investigator that any necessary additional therapeutic measures and follow-up procedures are performed. All adverse events must be monitored until their resolution or stabilization.

9. Statistical methods and sample size

9.1. Research question and hypothesis

The primary research question to be answered in this randomized controlled trial is whether FSRT (experimental arm) achieves significantly better local control than the "gold standard", single-fraction SRS (control group) in patients with large brain metastases. The time to local progression (TTLP) of the irradiated lesions will be used as the primary endpoint for efficacy. TTLP is defined as the time from randomization until the detection of progression as per the *RANO-BM* criteria (cf. Section 8.1 – 8.3). Patients will be censored if they have no signs of local progression at the time of last tumor monitoring during follow-up or at the onset of one of the following competing risk events not associated with, or preceded by local progression: death, lost to follow up, unauthorized non-protocol treatment of the target lesions. The following hypotheses will be tested:

H0: HR (FSRT vs. SRS as standard) ≥ 0

H1: HR (FSRT vs. SRS as standard) < 0

HR = Hazard ratio

One-sided testing of the primary endpoint will be performed based on the formulated hypotheses.

9.2. Sample size calculation

On the basis of available retrospective and dose-response relationship data, it is expected that SRS will result in a 12-month local tumor control rate of approximately 65% and that FSRT can increase this rate to about 80% (cf. Section 1.4). This difference is considered to be clinically significant. A sample size of N=191 evaluable cases each in the experimental and control arm, respectively, corresponding to a total of 382 patients, is required to detect a significant difference i.e. an increase in TTLP at least this large at 12-month follow-up in a randomized comparison. The number of TTLP events to be observed is 82. This calculation is based on the following framework conditions:

- The risk of making a false claim of superiority of FSRT which actually does not exist is 2.5% (α error, one-sided).
- The success rate for identifying superiority of FSRT over the control arm which actually exists is 80% (power, 1-β error).
- Assuming an exponential decline of TTLP curves
- As this is a basically palliative setting with disseminated disease, it must be considered that about half of the patients will be dead at 12-month follow-up. Consequently, a considerable proportion of patients

will have a truncated follow-up in which no event related to the primary endpoint occurs. The extent of this quasi-drop-out process is estimated to be ≤ 50% and is also assumed to be exponentially distributed over the 12 months.

- Duration of follow-up for all patients: at least 12 months or until the incidence of local progression.

Note: Due to patient entry kinetics during the planned recruitment, and due to the intended follow-up period of up to 24 months for each patient (cf. section 5.1.4), the follow-up periods for a considerably number of patients, mainly those randomized early, may be significantly longer than 12 months by the end of the study. This should result in an increase in the expected number of observed events, leading to a further increase in power of the study. Since this effect is difficult to quantify (especially due to death as a competing risk event), it is not taken into account in sample size calculation, to be on the safe side. Therefore, the recruitment period is not included among the parameters provided above.

Sample size estimates were calculated based on the method of LACHIN and FOULKES (Lachin et al. 1986), applying the software NSURV (idv, Gauting, Germany).

9.3. Patient evaluation categories

If a major eligibility violation occurs, the affected subject will be excluded from the statistical analysis and classified as "ineligible" (in accordance with the ICH E9 statistical principles for clinical trials). Only case reports will be presented for these patients.

All other patients will be included in an intention-to-treat analysis of the primary endpoint. A per-protocol analysis including only those patients who fully completed radiotherapy according to protocol will also be performed, as a sensitivity analysis.

All patients who received at least one dose of radiation treatment according to protocol will be included in the toxicity analysis.

9.4. Statistical analysis

Descriptive statistics will be used to check the balance of the treatment groups of the study population with regard to demographic and prognostic baseline data. Sensitivity analyses will be conducted if needed to adjust for relevant imbalances in the study population by appropriate modeling or stratification, including the corresponding co-variables. Adjusted and non-adjusted analyses will be compared and critically analyzed. With respect to the primary endpoint, the main analysis will account for the stratified randomization (stratified log-rank test).

Confirmatory analysis of the primary endpoint variable will be performed using a p-value of $p \leq 0.025$ (one-sided) as significance level.

All other parameters will be analyzed by descriptive statistics describing their frequencies, arithmetic means, standard deviations, median values, interquartile distances, ranges and, eventually, confidence intervals. If exploratory statistical analyses are performed for comparison of the different treatment arms or subgroups, p-values will be explicitly reported. As a rule, adjustment of significance levels for multiple analyses (multiplicity adjustment) will not be performed, so the p-values are considered to be descriptive and reflect a Type I error for the individual comparison and not for the overall experiment. Unless otherwise stated, two-sided tests will be used. The statistical methods listed below are usually suitable for the data and distributions expected in such studies. Their suitability will be assessed after data collection. If necessary, the choice of methods will be modified accordingly, and the respective results will be critically evaluated in a sensitivity analysis.

Toxicity and response rates as well as survival and progression-free survival rates at the specified time points will be calculated together with their exact confidence intervals and compared by either Fisher's Exact Test, the χ^2 Test or the Mantel-Haenszel test (Cochran-Armitage trend test), as appropriate for the type and extent of the variable.

The Wilcoxon-Mann-Whitney test will be used to test continuous data or scales in intergroup comparisons, and the Wilcoxon signed-rank test will be used to compare paired samples between different sampling times.

Time-to-event data such as time to local progression (TTLP), local progression-free survival (LPFS), and overall survival (OS) will be presented in life tables constructed using the KAPLAN-MEIER method (Kaplan et al. 1958) and compared using the log-rank test (Here, LPFS is defined like TTLP except that death not preceded by local progression will not be censored but counted as an event). If the assumption of "proportional hazards" underlying the Peto log rank test (Peto et al. 1972, Peto et al. 1976) clearly does not apply (Haybittle 1988), Gehan's generalized Wilcoxon test for comparing arbitrarily singly-censored samples will also be used as sensitivity analysis (Gehan 1965), preferably, as modified by Peto and co-workers and Prentice (Peto et al. 1972, Prentice 1978). Prospective stratification and other prognostic strata, if necessary, may be taken into account in further sensitivity analyses (Peto et al. 1976).

TTLP, the primary endpoint of the study, will be described and evaluated in another sensitivity analysis based on the cumulative incidence method (Gray 1988), in which death not associated with local progression will be treated as a competing risk event

Univariate consideration of prognostic factors will be performed by applying the above-mentioned methods accordingly. Multivariate analysis, if required, will be performed using the Cox proportional hazards regression model (Cox 1972).

Further details regarding the statistical analysis will be specified prospectively in a Statistical Analysis Plan before any analyses of treatment efficacy are carried out. As software, SPSS, R, TESTIMATE, and/or SQL will be used for analysis.

9.5. Interim analyses

A descriptive analysis of CNS adverse events, according to CTCAE v5.0, will be performed after recruitment of 50, 100 and 200 patients, respectively. No interim analyses for efficacy will be performed. As no interim analyses will be performed on any of the efficacy-related endpoints, the type I error of the trial is not affected. The DSMB will review the safety data and may terminate the trial in case of unexpected toxicities or unexpectedly high frequency of adverse events. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Details on the interim analyses will be described in the Statistical Analysis Plan and, in cooperation with the DSMB members, in a DSMB Charter.

10. Use of information and publication

For all publications, data protection is maintained for all patients as well as for the data of the participating investigators. Any documents supplied in connection with this study, and not previously published, are considered confidential information. This information includes the clinical protocol, workbooks if applicable, case report forms etc. This confidential information shall not be disclosed to others without prior written consent from the coordinating investigator and shall not be used except in the performance of this study. The information developed during the conduct of this clinical study is also considered confidential.

The results of the study will be published in scientific journals and presented at national and international congresses. The “Uniform requirements for manuscripts submitted to biomedical journals” (International Committee of Medical Journal Editors, ICMJE) will be respected.

As recommended by the ICMJE, the study has been registered in two public trials registries: ClinicalTrials.gov (www.clinicaltrials.gov) and at the German Clinical Trials Register (www.drks.de - DRKS00015647).

The authorship list will be determined by the scientific study director prior to publication.

The investigations carried out as part of the study, in particular MRI imaging data, may be used anonymously to answer future medical research questions not specified in the protocol.

11. Funding

This study is funded by the German Cancer Aid (Deutsche Krebshilfe, 70113619) and is partly financed by Universitätsklinikum Erlangen (University Hospital of Erlangen).

12. Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects (see § 10, Abs. 1 GCP-V for the decision criteria) will require a formal amendment to the protocol. Such amendment will be agreed upon by the investigators. It requires a new application to the appropriate ethical committees prior to implementation, according to §10, Abs. 2 to 4 GCP-V.

Administrative or technical changes of the protocol such as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, nor on the risk-benefit-ratio, will be agreed upon by the investigators and will be documented in a memorandum to the protocol. The appropriate ethical committees may be notified of such changes at the discretion of the study management or a delegated person/institution.

The study management or a delegated person/institution has to assure, that all amendments have been added to the study documents at any site involved in the trial.

13. References

Amsbaugh, M. J., et al. (2015). "Tumor bed radiosurgery: an emerging treatment for brain metastases." J Neurooncol 123(2): 197-203.

Anker, C. J., et al. (2016). "Avoiding Severe Toxicity From Combined BRAF Inhibitor and Radiation Treatment: Consensus Guidelines from the Eastern Cooperative Oncology Group (ECOG)." Int J Radiat Oncol Biol Phys 95(2): 632-646.

Aoyama, H., et al. (2006). "Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial." JAMA 295(21): 2483-2491.

Arita, H., et al. (2018). "Lesion location implemented magnetic resonance imaging radiomics for predicting IDH and TERT promoter mutations in grade II/III gliomas." Scientific Reports 8(1): 11773.

Arrieta, O., et al. (2011). "Long-term survival in patients with non-small cell lung cancer and synchronous brain metastasis treated with whole-brain radiotherapy and thoracic chemoradiation." Radiat Oncol 6: 166.

AWMF (2015). "Hirnmetastasen und Meningeosis neoplastica." from https://www.awmf.org/leitlinien/detail/ll/030-060.html.

Badiyan, S. N., et al. (2016). "Stereotactic Radiosurgery for Treatment of Brain Metastases." J Oncol Pract 12(8): 703-712.

Baumert, B. G., et al. (2006). "A pathology-based substrate for target definition in radiosurgery of brain metastases." Int J Radiat Oncol Biol Phys 66(1): 187-194.

Berghoff, A. S., et al. (2013). "Invasion patterns in brain metastases of solid cancers." Neuro Oncol 15(12): 1664-1672.

Blonigen, B. J., et al. (2010). "Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery." Int J Radiat Oncol Biol Phys 77(4): 996-1001.

Brown, P. D., et al. (2016). "Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial." JAMA 316(4): 401-409.

Carlson, J. A., et al. (2014). "Trastuzumab emtansine and stereotactic radiosurgery: an unexpected increase in clinically significant brain edema." Neuro Oncol 16(7): 1006-1009.

Chao, J. H., et al. (1954). "Roentgen-ray therapy of cerebral metastases." Cancer 7(4): 682-689.

Chao, S. T., et al. (2013). "Challenges with the diagnosis and treatment of cerebral radiation necrosis." Int J Radiat Oncol Biol Phys 87(3): 449-457.

Chao, S. T., et al. (2008). "Salvage stereotactic radiosurgery effectively treats recurrences from whole-brain radiation therapy." Cancer 113(8): 2198-2204.

Chargari, C., et al. (2011). "Preliminary results of whole brain radiotherapy with concurrent trastuzumab for treatment of brain metastases in breast cancer patients." Int J Radiat Oncol Biol Phys 81(3): 631-636.

Chargari, C., et al. (2009). "Concurrent capecitabine and whole-brain radiotherapy for treatment of brain metastases in breast cancer patients." J Neurooncol 93(3): 379-384.

Chen, L., et al. (2018). "Concurrent Immune Checkpoint Inhibitors and Stereotactic Radiosurgery for Brain Metastases in Non-Small Cell Lung Cancer, Melanoma, and Renal Cell Carcinoma." Int J Radiat Oncol Biol Phys 100(4): 916-925.

Chen, L. K., et al. (2012). "Chemotherapy with concurrent brain and thoracic radiotherapy in brain-only metastases of treatment naive small-cell lung cancer: a phase II study." Med Oncol 29(3): 1687-1692.

Cox, D. R. (1972). "Regression Models and Life-Tables." Journal of the Royal Statistical Society. Series B (Methodological) 34(2): 187-220.

Dinglin, X. X., et al. (2013). "Pemetrexed and cisplatin combination with concurrent whole brain radiotherapy in patients with brain metastases of lung adenocarcinoma: a single-arm phase II clinical trial." J Neurooncol 112(3): 461-466.

Distel, L. V. R., et al. (2006). "Individual differences in chromosomal aberrations after in vitro irradiation of cells from healthy individuals, cancer and cancer susceptibility syndrome patients." Radiotherapy and Oncology 81(3): 257-263.

Eaton, B. R., et al. (2015). "Hypofractionated radiosurgery has a better safety profile than single fraction radiosurgery for large resected brain metastases." J Neurooncol 123(1): 103-111.

Ernst-Stecken, A., et al. (2006). "Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: results and toxicity." Radiother Oncol 81(1): 18-24.

Fokas, E., et al. (2012). "Stereotactic radiosurgery and fractionated stereotactic radiotherapy: comparison of efficacy and toxicity in 260 patients with brain metastases." J Neurooncol 109(1): 91-98.

Furuse, K., et al. (1997). "A pilot study of concurrent whole-brain radiotherapy and chemotherapy combined with cisplatin, vindesine and mitomycin in non-small-cell lung cancer with brain metastasis." Br J Cancer 75(4): 614-618.

Furuse, M., et al. (2015). "Delayed brain radiation necrosis: pathological review and new molecular targets for treatment." Medical Molecular Morphology 48(4): 183-190.

Gehan, E. A. (1965). "A Generalized Wilcoxon Test for Comparing Arbitrarily Singly-Censored Samples." Biometrika 52: 203-223.

Geraud, A., et al. (2017). "Preliminary experience of the concurrent use of radiosurgery and T-DM1 for brain metastases in HER2-positive metastatic breast cancer." J Neurooncol 131(1): 69-72.

Gray, R. J. (1988). "A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk." Ann. Statist. 16(3): 1141-1154.

Haybittle, J. L. (1988). Significance Testing in the Comparison of Survival Curves from Clinical Trials of Cancer Treatment. Cancer Clinical Trials, Berlin, Heidelberg, Springer Berlin Heidelberg.

Higuchi, Y., et al. (2009). "Three-staged stereotactic radiotherapy without whole brain irradiation for large metastatic brain tumors." Int J Radiat Oncol Biol Phys 74(5): 1543-1548.

Huang, Y. J., et al. (2007). "Weekly gemcitabine as a radiosensitiser for the treatment of brain metastases in patients with non-small cell lung cancer: phase I trial." Chin Med J (Engl) 120(6): 458-462.

ICRU (2017). "Report 91." Journal of the International Commission on Radiation Units and Measurements 14(2): 1-160.

Joiner (2009). Quantifying cell kill and survival. Basic clinical radiobiology. v. d. K. A. Joiner M. London, England, Hodder Arnold.

Kallman, R. F. (1972). "The phenomenon of reoxygenation and its implications for fractionated radiotherapy." Radiology 105(1): 135-142.

Kaplan, E. L. and P. Meier (1958). "Nonparametric Estimation from Incomplete Observations." Journal of the American Statistical Association 53(282): 457-481.

Kaufmann, T. J., et al. (2020). "Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases." Neuro Oncol 22(6): 757-772.

Kiess, A. P., et al. (2015). "Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment." Int J Radiat Oncol Biol Phys 92(2): 368-375.

Kim, Y. J., et al. (2011). "Single-dose versus fractionated stereotactic radiotherapy for brain metastases." Int J Radiat Oncol Biol Phys 81(2): 483-489.

Kirkpatrick, J. P., et al. (2015). "Defining the optimal planning target volume in image-guided stereotactic radiosurgery of brain metastases: results of a randomized trial." Int J Radiat Oncol Biol Phys 91(1): 100-108.

Kocher, M., et al. (2011). "Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study." J Clin Oncol 29(2): 134-141.

Kocher, M., et al. (2014). "Stereotactic radiosurgery for treatment of brain metastases. A report of the DEGRO Working Group on Stereotactic Radiotherapy." Strahlenther Onkol 190(6): 521-532.

Kondziolka, D., et al. (2015). "The biology of radiosurgery and its clinical applications for brain tumors." Neuro Oncol 17(1): 29-44.

Kroeze, S. G., et al. (2017). "Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review." Cancer Treat Rev 53: 25-37.

Levin, V. A., et al. (2011). "Randomized Double-Blind Placebo-Controlled Trial of Bevacizumab Therapy for Radiation Necrosis of the Central Nervous System." International Journal of Radiation Oncology*Biology*Physics 79(5): 1487-1495.

Levy, C., et al. (2014). "REBECA: a phase I study of bevacizumab and whole-brain radiation therapy for the treatment of brain metastasis from solid tumours." Ann Oncol 25(12): 2351-2356.

Lin, N. U., et al. (2015). "Response assessment criteria for brain metastases: proposal from the RANO group." Lancet Oncol 16(6): e270-278.

Mathew, M., et al. (2013). "Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery." Melanoma Res 23(3): 191-195.

Matsuyama, T., et al. (2013). "Clinical outcomes of biological effective dose-based fractionated stereotactic radiation therapy for metastatic brain tumors from non-small cell lung cancer." Int J Radiat Oncol Biol Phys 85(4): 984-990.

Minniti, G., et al. (2016). "Single-Fraction Versus Multifraction (3 x 9 Gy) Stereotactic Radiosurgery for Large (>2 cm) Brain Metastases: A Comparative Analysis of Local Control and Risk of Radiation-Induced Brain Necrosis." Int J Radiat Oncol Biol Phys 95(4): 1142-1148.

Mitsuya, K., et al. (2016). "Expansive hematoma in delayed cerebral radiation necrosis in patients treated with T-DM1: a report of two cases." BMC Cancer 16: 391.

Molenaar, R., et al. (2009). "Relationship between volume, dose and local control in stereotactic radiosurgery of brain metastasis." Br J Neurosurg 23(2): 170-178.

Narayana, A., et al. (2007). "Hypofractionated stereotactic radiotherapy using intensity-modulated radiotherapy in patients with one or two brain metastases." Stereotact Funct Neurosurg 85(2-3): 82-87.

NCCN (2021). "Central Nervous System Cancers (Version 2.2021)." Retrieved 07.10.2021, from https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.

Oft, D., et al. (2020). "Volumetric Regression in Brain Metastases After Stereotactic Radiotherapy: Time Course, Predictors, and Significance." Front Oncol 10: 590980.

Peto, R. and J. Peto (1972). "Asymptotically Efficient Rank Invariant Test Procedures." Journal of the Royal Statistical Society. Series A (General) 135(2): 185-207.

Peto, R., et al. (1976). "Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design." Br J Cancer 34(6): 585-612.

Prentice, R. L. (1978). "Linear rank tests with right censored data." Biometrika 65(1): 167-179.

Putz, F., et al. (2020). "Magnetic resonance imaging for brain stereotactic radiotherapy : A review of requirements and pitfalls." Strahlenther Onkol 196(5): 444-456.

Putz, F., et al. (2020). "FSRT vs. SRS in Brain Metastases-Differences in Local Control and Radiation Necrosis-A Volumetric Study." Front Oncol 10: 559193.

Quantin, X., et al. (1999). "Concomitant brain radiotherapy and vinorelbine-ifosfamide-cisplatin chemotherapy in brain metastases of non-small cell lung cancer." Lung Cancer 26(1): 35-39.

Rühle, P., et al. (2016). "Development of a Modular Assay for Detailed Immunophenotyping of Peripheral Human Whole Blood Samples by Multicolor Flow Cytometry." International Journal of Molecular Sciences 17(8): 1316.

Rühle, P. F., et al. (2017). "Modulations in the Peripheral Immune System of Glioblastoma Patient Is Connected to Therapy and Tumor Progression-A Case Report from the IMMO-GLIO-01 Trial." Front Neurol 8: 296.

Schmitt, D., et al. (2020). "Technological quality requirements for stereotactic radiotherapy : Expert review group consensus from the DGMP Working Group for Physics and Technology in Stereotactic Radiotherapy." Strahlenther Onkol 196(5): 421-443.

Seymour, Z. A., et al. (2015). "Interval From Imaging to Treatment Delivery in the Radiation Surgery Age: How Long Is Too Long?" Int J Radiat Oncol Biol Phys 93(1): 126-132.

Shaw, E., et al. (1993). "Radiation Therapy Oncology Group: radiosurgery quality assurance guidelines." Int J Radiat Oncol Biol Phys 27(5): 1231-1239.

Shaw, E., et al. (2000). "Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05." Int J Radiat Oncol Biol Phys 47(2): 291-298.

Soffietti, R., et al. (2017). "Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO)." Neuro Oncol 19(2): 162-174.

Tsao, M. N., et al. (2012). "Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline." Pract Radiat Oncol 2(3): 210-225.

Verduin, M., et al. (2017). "Use of Systemic Therapy Concurrent With Cranial Radiotherapy for Cerebral Metastases of Solid Tumors." Oncologist 22(2): 222-235.

Vogelbaum, M. A., et al. (2006). "Local control of brain metastases by stereotactic radiosurgery in relation to dose to the tumor margin." J Neurosurg 104(6): 907-912.

Wiggenraad, R., et al. (2011). "Dose-effect relation in stereotactic radiotherapy for brain metastases. A systematic review." Radiother Oncol 98(3): 292-297.

Withers, H. (1975). The Four R's of Radiotherapy. Advances in Radiation Biology. L. J. Adler H, Zelle M. New York, Academic Press. 5: 241–247.

Xi, Y. B., et al. (2018). "Radiomics signature: A potential biomarker for the prediction of MGMT promoter methylation in glioblastoma." J Magn Reson Imaging 47(5): 1380-1387.

Yang, R., et al. (2018). "Inhibitors of HIF-1α and CXCR4 Mitigate the Development of Radiation Necrosis in Mouse Brain." International Journal of Radiation Oncology*Biology*Physics 100(4): 1016-1025.

Yomo, S., et al. (2013). "Impacts of HER2-overexpression and molecular targeting therapy on the efficacy of stereotactic radiosurgery for brain metastases from breast cancer." J Neurooncol 112(2): 199-207.

Zindler, J. D., et al. (2018). "Improved effectiveness of stereotactic radiosurgery in large brain metastases by individualized isotoxic dose prescription: an in silico study." Strahlenther Onkol 194(6): 560-569.

14. Appendix FSRT Trial

Patient informed consent 1.16, 02.12.2022