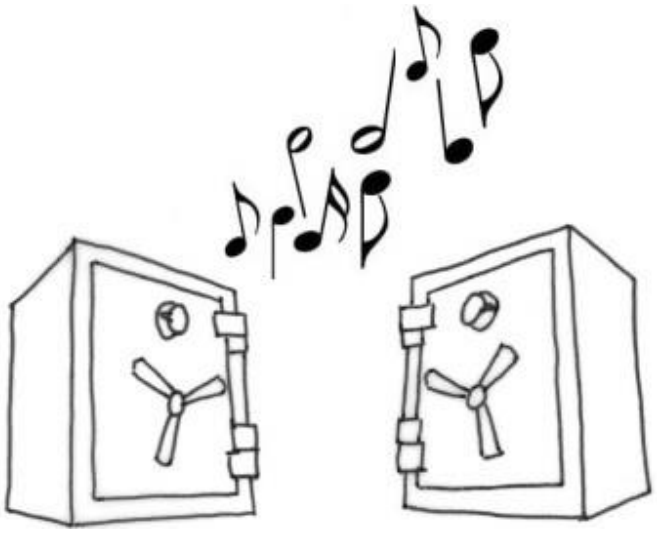
RESEARCH PROTOCOL



PROTOCOL TITLE 'Improving therapeutic ratio with hypofractionated stereotactic radiotherapy for brain metastases.'

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Date	**14-11-2023**
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Laboratory sites <*if applicable*>	**N/A**
Pharmacy <*if applicable*>	**N/A**

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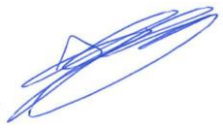
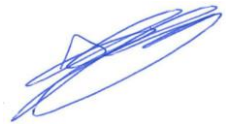
Sponsor or legal representative: Dr. Jaap Zindler, MD, PhD, radiation oncologist		**14-11-2023**
Coordinating Investigator: Dr. Jaap Zindler, MD, PhD, radiation oncologist		**14-11-2023**

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AED	**Anti-epileptic drugs**
ALE	**Adverse local event**
BED	**Biologically effective dose**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CTCAE	**Common Terminology Criteria for Adverse Events**
CTV	**Clinical target volume**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EORTC	**European Organisation for Research and Treatment of Cancer**
EPTN	**European Particle Therapy Network**
EudraCT	**European drug regulatory affairs Clinical Trials**
Gd	**Gadolinium**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
GTV	**Gross tumor volume**
fSRT	**Hypofractionated stereotactic radiotherapy**
HRQoL	**Health-related quality of life**
IADL	**Instrumental activities of daily living**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICH	**International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use**
KPS	**Karnofsky performance status**
LINAC	**Linear accelerator**
LPRNO	**National Platform Radiotherapy and Neuro-oncology in the Netherlands; in Dutch: Landelijk Platform Radiotherapie en Neuro-oncologie**

METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MRI	**Magnetic resonance imaging**
OAR(s)	**Organ(s) at risk**
PI	**Principal investigator**
PTV	**Planning target volume**
RANO	**Response Assessment in Neuro-Oncology**
RANO-BM	**Response Assessment in Neuro-Oncology Brain Metastases**
RLIES	**Revised Liverpool Impact of Epilepsy Scale**
(S)AE	**(Serious) Adverse Event**
SRT	**Stereotactic radiotherapy**
Sponsor	**The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
V12Gy	**Tissue volume receiving a dose of at least 12Gy**
WBRT	**Whole brain radiotherapy**
WHO-PS	**World Health Organization performance status**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Stereotactic radiotherapy is one of the most frequently chosen treatment options for brain metastases. There are an increasing number of long term survivors. Brain necrosis (e.g. radionecrosis) is the most important long term side effect of the treatment, occurring in up to 40% of patients, dependent on the size of the metastasis and delivered radiotherapy dose. Retrospective studies have shown that the incidence of radionecrosis, as well as local tumor recurrence, can be decreased with a risk difference of around 20% by administrating fractionated stereotactic radiotherapy (fSRT, e.g. five fractions) over single fraction stereotactic radiotherapy, especially in large brain metastases.

Objective: To determine if the incidence of adverse local events (local failure or radionecrosis) can be reduced with more than 20% using fSRT versus SRT in one or three fractions.

Study design: Prospective, multicenter, open label, randomized, phase II study with two cohorts.

Study population: Patients, 18 years and older, with one or more brain metastases from solid primary tumors diagnosed on a high resolution contrast-enhanced MRI scan referred for stereotactic radiotherapy.

Intervention (if applicable): One group is treated with SRT in one or three fractions. The other group is treated with fSRT in five fractions.

Main study parameters/endpoints: The main study parameter is the incidence of adverse local event (either local failure or radionecrosis according to RANO) at 2 years post-radiotherapy with respect to baseline.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The study aims to investigate a different and potentially safer treatment method than the current standard of care. It is unlikely that the risk of adverse events will be increased in the experimental cohort compared to the standard cohort. The additional burden as a result of study participation consists of the following: between two and four additional site visits for treatment in the experimental group; a total of eighteen (facultative) questionnaires spread throughout the follow-up period.

1. INTRODUCTION AND RATIONALE

Since publication of the QUARTZ trial, the palliative benefit and indication of whole brain radiotherapy (WBRT) is a matter of debate for patients with brain metastases.[1] After WBRT, patients may suffer from alopecia, fatigue, and there is a risk of neurocognitive dysfunction caused by the elective brain irradiation. In phase III trials, (elective) WBRT has never shown benefit in survival nor health-related quality of life in large cell cancer histologies.[2]

In the last decades, effective alternative treatments for brain metastases have become available. Targeted agents and/or immunotherapy have shown to effectively treat brain metastases in several subtypes of cancer. Stereotactic radiotherapy (SRT) has become widely available, also for multiple brain metastases.[3] SRT has shown to treat brain metastases more effectively with a higher probability of local tumor control than WBRT. Moreover, elective brain irradiation is avoided and thereby side effects of WBRT. Because of publication of the favorable results in terms of local tumor control and median survival of large cohorts of patients with SRT also in patients up to ten brain metastases with low volume disease, several international guidelines (UK NICE guideline, American neurosurgery guideline) state that SRT is also a treatment option for patients with more than three brain metastases.[4] This advice is also stated in the revised Dutch guideline for brain metastases, that radiosurgery is a treatment option for patients up to 10 brain metastases with a maximum individual volume of the brain metastases of 20 cm^3 and a maximum cumulative volume of 30 cm^3.[5] In the current era of personalized medicine, the main question is how to integrate SRT into the multimodality treatment for brain metastases with systemic therapies and surgery. This is complex and decided in the multidisciplinary board.[6]

As clinicians, we observe an increasing number of long term survivors over several years with brain metastases. Brain necrosis or radionecrosis is a long term side effect of SRT which occurs in +/-20% of patients and the incidence may increase up to +/-40% if SRT is combined with immunotherapy.[7] Radionecrosis may cause neurologic symptoms, such as focal neurological deficits, neurocognitive dysfunction and seizures, which require treatment with steroids, bevacuzimab, or sometimes even surgery. SRT is mostly delivered with an ablative high radiotherapy dose in a single fraction. In the first millimeters close to the brain metastasis, the healthy brain tissue receives a high dose as well.

In radiotherapy literature, it is known that more fractionated radiotherapy, e.g. hypofractionated radiotherapy (fSRT), may decrease side effects. fSRT means delivering the ablative dose in multiple fractions (f.e. 5 fractions) over several days instead of delivering the ablative dose within half an hour.[8] Recent retrospective studies showed that risk difference of local failure and radionecrosis is almost 30% in larger tumors (>2.5 cm; constituting around

50% of metastases), while the incidence is equivalent in smaller metastases.[9,10, 22] To achieve a local control of more than 90% after one year, it is important to deliver a cumulative biologically effective dose (BED) of at least 50 Gy. 35 Gy in 5 fractions results in a BED of more than 50Gy.[11,12] Another potential benefit of fSRT over SRT in one or three fractions is better induction of an abscopal effect. SRT in one or three fractions results in massive tumor necrosis. fSRT may result in more regulated cell death: apoptosis, with better antigen presentation of dying tumor cells. It is hypothesized that this may subsequently result in better activation of the immune cells against the cancer and better control of micrometastases outside the irradiation field.[13] Several studies are ongoing in which SRT is combined with immunotherapy to increase systemic tumor control and thereby improve survival.[14]

2. OBJECTIVES

Primary Objective: To determine if the percentage of adverse local events (either local failure or radionecrosis) can be reduced by using fSRT versus SRT in one or three fractions 2 years post-SRT.
Secondary Objective(s): To investigate if fSRT provides better quality of life and lower incidence of epilepsy versus SRT in one or three fractions. Additionally, to estimate overall survival as well as the cumulative incidence of local failure or radionecrosis with death as competing risk.

3. STUDY DESIGN

The study is a prospective randomized cohort study with two study cohorts. Patients are allocated to a study cohort by randomization. The follow-up will be two years. The study will take place in a multicenter clinical setting.

Patients from the two study cohorts will receive a different fractionation treatment schedule. Patients in the standard cohort will receive SRT in one or three fractions according to the Dutch guideline (consensus Landelijk Platform Radiotherapie en Neuro-oncologie; LPRNO), while patients in the experimental cohort will receive fSRT in five fractions.

The planned duration is as follows:
Data collection: March 2022-March 2027 (3 years for patient inclusion, 2 years follow-up)
Statistical analyses: March 2027
Writing article: April 2027-June 2027
NB: these dates are an estimate and are dependent on several factors, such as approval from the ethics and research commissions.

4. STUDY POPULATION

4.1 Population (base)

Patients (≥18 years old) with one or more brain metastases from solid primary tumors diagnosed on a high resolution contrast-enhanced MRI scan referred for SRT in Dutch hospitals.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years
- At least one brain metastasis of large cell cancer suitable for SRT
- Karnofsky Performance Status ≥ 70
- Ability to provide written informed consent
- Previous systemic therapy for brain metastases allowed
- New brain metastases during follow-up after surgery allowed (outside resection cavity)

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Contra-indication for MRI scan
- Primary tumor of small cell lung cancer, germinoma or lymphoma
- Prior whole brain radiotherapy or SRT on the current target brain metastases (BM) (in field re-irradiation; salvage SRT of non-irradiated BM allowed if radiation dose from previous irradiation in current target field is <1.0 Gy)
- Presence of leptomeningeal metastases
- Previous inclusion in the SAFESTEREO study

4.4 Sample size calculation

Standard cohort: Mean risk of local failure or radionecrosis 1 year = 30%
Experimental cohort: Mean risk of local failure or radionecrosis experimental arm @ 1 year = 10%
Enrollment ratio standard vs experimental cohort 1:1
Alpha = 0.05
Power=0.8
Sample size standard arm n=59
Sample size experimental arm n=59
Minimum number of patients required for the study: 118
Number of patients including additional 10% to account for missing data: 130

These number were based on the following power analysis and were calculated with PASS® software (NCSS Statistical Software):

The results are based on the exact binomial test:
Numeric results of tests based on the difference: P1 - P2
H0: P1 - P2 = 0. H1: P1 - P2 = D1≠0. Test Statistic: Z test with pooled variance.

Power	Sample size group 1 (N1)	Sample size group 2 (N2)	Prop|H1 Group 1 (P1)	Prop Group 2 (P2)	Diff if H0 (D0)	Diff if H1 (D1)	Target alpha	Actual alpha	Beta
0.8051	59	59	0.3000	0.1000	0.000	0.200	0.0500	0.0507	0.1949

Note: exact results based on the binomial were only calculated when both N1 and N2 were less than 100.

The total number of patients with brain metastases treated at the department of radiotherapy in our hospital in 2019 was around 150, of whom an estimated 135 would have been eligible for inclusion. Therefore, a 3-year period (as mentioned in paragraph 3) should be sufficient to include enough patients.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The investigational treatment is SRT delivered in five fractions. This treatment is described in more detail in paragraphs 8.3.1-8.3.9. The standard treatment of stereotactic radiotherapy delivered in one or three fractions is also described in those paragraphs.

5.2 Use of co-intervention (if applicable)

N/A

5.3 Escape medication (if applicable)

N/A

6. INVESTIGATIONAL PRODUCT

The study does not include use of a medicinal product, food product, medical device or other product. Therefore, this chapter is not applicable.

7. NON-INVESTIGATIONAL PRODUCT

No challenge agents or products used to assess endpoints are used in the trial. Therefore, this chapter is not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Incidence of adverse local event (ALE) at 2 years post-radiotherapy with respect to baseline.

Definition of ALE = either radionecrosis or local failure according to Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM).[15, 22]

Definition of radionecrosis = increasing size and low perfusion MR by interpretation of a dedicated radiologist (multidisciplinary board).

Definition of local failure is ≥20% increase in sum longest distance relative to nadir in target lesion.

8.1.2 Secondary study parameters/endpoints

- Survival time/survival at 2 years post-SRT
- Incidence of symptomatic radionecrosis
- Incidence of symptomatic local failure
- Incidence of salvage treatments at 2 years post-SRT
- Distant brain recurrences at 2 years post-SRT
- Dose dexamethasone at baseline, 3 months after radiotherapy and thereafter every three months until 2 years
- Anti-epileptic drug (AED) use
- Bevacizumab use
- Grade 2 or more toxicity (CTCAE v5.0)
    - Alopecia, cognitive symptoms, fatigue, dysphasia, hearing loss, visual impairment, generalized muscle weakness

8.1.3 Other study parameters

Facultative endpoints:

- HRQoL (measured with EORTC QLQ-C30 and QLQ-BN20) at baseline, 3, 6, 12, 18 and 24 months after radiotherapy
- IADL (measured with EQ-5D 5L) at baseline, 3, 6, 12, 18 and 24 months after radiotherapy

8.2 Randomization, blinding and treatment allocation

Patients who meet the inclusion criteria (see paragraph 4.2) can be included in the study after consultation with the radiation oncologist and after they have signed informed consent. They will be randomized into either of the two cohorts.

Blinding of the groups cannot be performed, because the planning system needs to calculate the treatment time based on the fractionation schedule, which is determined by randomization. The involved employees of the radiation department need to process the data in the radiation therapy software and they need to carry out QA checks on the radiation treatment plans. The latter can only be performed if all information is available.

Patients who are randomized into the standard treatment group will receive the treatment as currently advised by the LPRNO guidelines. Patients will receive 1 fraction of SRT, unless it concerns a large tumor in proximity to the brainstem or a large tumor in proximity to other metastases, see paragraph 8.3.3. Based on previous literature, local progression or survival outcome are comparable for SRT in 1 or 3 fractions.[16]

Randomization to either SRS (1 or 3 fractions, see paragraph 8.3.3) or fSRT (5x7Gy or 5x6 Gy if in brainstem, see paragraph 8.3.3) will be 1:1, stratified by institute with block sizes 4 and 6.

8.3 Study procedures

Procedures which are part of the standard medical treatment are summarized in paragraphs 8.3.1-8.3.9. Measurements which are specifically measured for this study are listed in paragraph 8.3.10. A study flow chart is shown in figure 1. A treatment summary table, including an overview of what is and is not part of standard of care, is shown in table 1.

Figure 1: Study flow chart

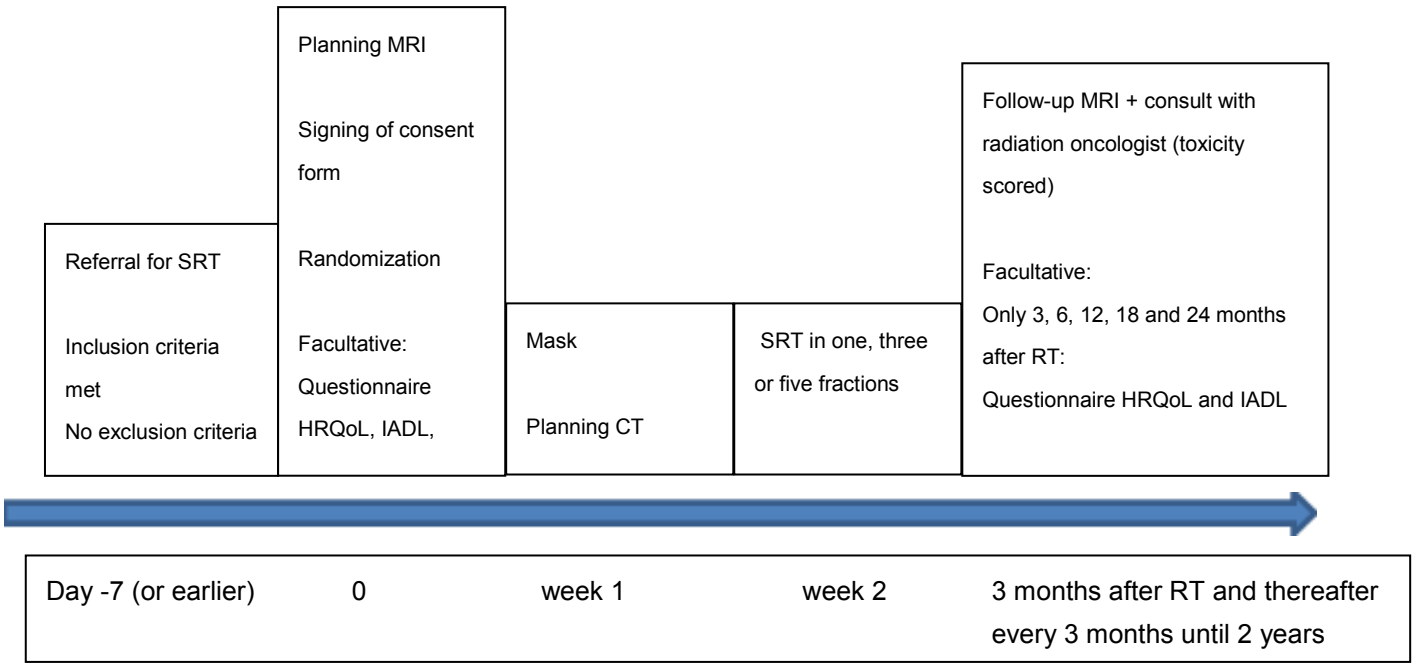

Table 1 Study parameter summary table

			Months post (f)SRT							
	Baseline	End of RT	3M	6M	9M	12M	15M	18M	21M	24M
Standard clinical care:										
Clinical characteristics: year of birth, gender, primary tumor type, presence of extracranial visceral metastases, primary tumor control, date diagnosis primary tumor, type of systemic therapy **Coded data** (see paragraph 12.1): patient number in electronic patient dossier	X									
Planning MRI & CT: number of brain metastases, total volume of brain metastases, volume of largest brain metastases	X									
Treatment characteristics: GTV largest metastasis, PTV largest metastasis, total volume GTV of all metastases, and total volume PTV of all metastases. Maximum dose in the PTV in anymetastasis. Maximum dose brain stem, chiasm, and optic nerves		X								
Physical examination	X									
WHO-PS and/or KPS	X									
Standard follow-up:										
Follow-up MRI: adverse local event (either radionecrosis or local failure according to RANO), distant brain recurrences			X	X	X	X	X	X	X	X
Toxicity (CTCAE v5.0)			X	X	X	X	X	X	X	X
Not part of standard follow-up:										
HRQoL (EORTC QLQ-C30, QLQ-BN20)	X		X	X		X		X		X
IADL (EQ-5D 5L)	X		X	X		X		X		X
Other follow-up:										
Use of dexamethasone or bevacizumab	X		X	X	X	X	X	X	X	X
Use of AED	X		X	X	X	X	X	X	X	X
Salvage treatment, type of salvage treatment, date of salvage treatment						X				X
Alive/dead			X	X	X	X	X	X	X	X
Symptomatic radionecrosis or local failure			X	X	X	X	X	X	X	X

8.3.1 MR imaging before SRT

The definitive number of brain metastases and the definitive maximum lesion diameter any direction of the largest brain metastasis is determined on contrast-enhanced (single - triple dose Gd is allowed) T1-sequences, maximum slice thickness 1.5 mm, field strength (1.0-3.0 Tesla with a 3D-distortion correction protocol.

8.3.2 Cessation of systemic treatments during SRT

The combination of SRT with several systemic cancer treatments, namely gemcitabine, erlotinib, vemurafenib and trastuzumab-emtansine, has been reported to increase the risk of radionecrosis. Therefore, these systemic treatments are halted at least one week before the first fraction until at least one week after the last fraction. Immunotherapy can be continued during SRT. All other systemic treatments are halted at least three days before the first fraction until at least three days after the last fraction. All the above is in accordance with the Dutch guidelines for treatment of brain metastases (https://richtlijnendatabase.nl/richtlijn/hersenmetastasen/startpagina_-_hersenmetastasen.html).

8.3.3 Fractionation schedule and radiation dose before SRT

Patients randomized into the experimental fSRT cohort receive a fractionation schedule based on “Working Agreement for uniform dose prescription stereotactic (LINAC) irradiation of brain metastases, Dutch Platform of Neuro Oncology”. This is 35 Gy in five fractions, or 30 Gy in five fractions if the metastasis is situated in the brainstem.

Patients randomized into the standard cohort will receive a fractionation schedule based on “Working Agreement for uniform dose prescription stereotactic (LINAC) irradiation of brain metastases, Dutch Platform of Neuro Oncology”. This is in the range of 15 Gy in a single fraction up to a 24 Gy in three fractions.

The dose gradient outside the PTV will be as steep as possible to spare healthy brain tissue. Within the PTV there will be considerable dose inhomogeneity

Dose prescription to brain metastases

PTV of brain metastases	**Dose 1 fraction**	**BM in brainstem (GTV=PTV)**	**Dose 5 fractions (Gy)**	**BM in brainstem (GTV=PTV)**
<1 cm^3	24	16	35	30
1-10 cm^3	21	16	35	30
10-20 cm^3	18	16	35	30
20-65 cm^3	15 or 3X8Gy	No SRS	35	30

Organ at risk constraints

	1 fraction (Gy) Optimal	1 fraction (Gy) Mandatory	D_{max} 3 fractions (Gy) Optimal	D_{max} 3 fractions (Gy) Mandatory	D_{max} 5 fractions (Gy) Optimal	D_{max} 5 fractions (Gy) Mandatory
Brainstem D_{max}	10	18	24	27	23	30
Cochlea D_{mean}	4	9	17	20	22	25
Chiasm D_{max}	8	10	15	23	20	25
Lens D_{max}	1	3	2	4	3	5
Optic nerves D_{max}	8	10	15	23	22	25
Pituary gland D_{mean}	8	10	15	23	22	25

Acceptable and unacceptable variation in dose

Volume	Per protocol D (Gy)	Acceptable variation	Unacceptable variation
PTV	$V_{100\%}$ = 99%	98%<$V_{100\%}$<99%	$V_{100\%}$<98%
D_{max} OAR if volume of OAR<2cm^3	0.035 cm^3	$D_{0.035cm3} \leq D_{max}$	$D_{0.035cc} > D_{max}$
D_{max} OAR if volume of OAR≥2cm^3	2%	$D_{2\%} \leq D_{max}$	$D_{2\%} > D_{max}$

8.3.4 GTV and OARs

The GTV is defined by contouring the outer contrast-enhancing border of the brain metastasis on a T1 Gd weighted MRI scan. Brain metastases are named GTV1, GTV2, GTV3, etc. from cranial to caudal. OARs (brainstem, optic nerves, chiasm, pituitary gland, etc.) are contoured according to EPTN consensus.[17]

8.3.5 SRT PTV

The PTV is defined by a 0-2 mm isotropic expansion of the GTV, according to institutional standards for SRT. If a brain metastasis is within or adjacent to the brainstem, the PTV margin will be 0 mm. If in an institution a smaller GTV to PTV margin is used when lesions are treated using multiple isocenters, then this technique is to be considered to reduce the V12Gy of the largest brain metastasis if it would otherwise be more than 10 cm^3.

8.3.6 SRT planning procedure

Patients will be immobilized in supine position wearing a thermoplastic mask or stereotactic non-invasive frame, with or without bite block and/or other fixation, according to institutional standards for SRT. The accuracy of the stereotactic fixation system should be sufficient to justify the CTV to PTV margin used. This means the intrafraction motion should at least be within the CTV-PTV margin used. If a margin of 0 mm is used, the maximum intrafraction motion should be <0.5 mm, with the SD being less than 0.25 mm. A planning CT scan with

≤2 mm thick contiguous slices (preferable CT slice thickness = 1mm) will be fused to a contrast-enhanced stereotactic MRI scan. The interval between the planning-MRI and actual SRT treatment is a maximum of 3 weeks.

8.3.7 SRT treatment technique

Single or multiple isocenters are allowed for delivering SRT according to the treating center preference. Tissue density inhomogeneity correction will be used. Positional verification and correction prior to (and/or during) radiation should be executed according to the institutional protocol for stereotactic radiotherapy and should be in accordance with the CTV-PTV margin used. All techniques that result in the dose requirements being met are allowed. Participating institutes will have to define their radiation delivery treatment prior to the initiation of the study. Techniques that have a shorter treatment time duration are preferred as this is more comfortable for the patient and might prevent an increase of the intrafraction displacement over the treatment time.

8.3.8 Dose reporting SRT

Tumor volume and treatment plan characteristics are reported (maximum dose, prescribed dose, and dose in critical organs at risk).

8.3.9 MR imaging after SRT

Tumor response evaluation as well as presence of distant brain recurrences are monitored every three months after SRT on contrast-enhanced (single - triple dose Gd is allowed) T1-sequences, maximum slice thickness 3 mm, field strength (1.0-3.0 Tesla with a 3D-distortion correction protocol including perfusion MR).

8.3.10 Questionnaires and other measurements

The following facultative questionnaires will be assessed at baseline, 3 months, 6 months, and 12 months, 18 months and 24 months after SRT: HRQoL (measured with EORTC QLQ-C30 and QLQ-BN20) and IADL (measured with EQ-5D 5L).
Toxicity (according to CTCAE v5.0) and use of AED, dexamethasone and bevacizumab is evaluated at baseline, 3 months after SRT and thereafter every three months until 2 years via telephone or during scheduled outpatient clinic visits. Need for salvage treatments, or symptomatic radionecrosis, and survival are all evaluated 2 years after SRT.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

If a subject becomes incapacitated during the study period, and if it will no longer be possible to make MRI scans, to send questionnaires, to evaluate toxicity, etc. In such a case, the same guidelines are followed as described for subjects who withdraw from the study for any reason (see 8.5 and 8.6).

8.4.1 Specific criteria for withdrawal (if applicable)

N/A

8.5 Replacement of individual subjects after withdrawal

With respect to patients applicable for this study willing to participate, and who have signed informed consent (paragraph 11.2): before randomization any patient will be replaced if the patient withdraws for any reason. These patients are not included in the statistical analysis. After the randomization, patients withdrawing for any reason will not be substituted by additional patients and these patients are analyzed by intention to treat.

8.6 Follow-up of subjects withdrawn from treatment

Patients who withdraw after randomization will not be requested to participate for follow-up questionnaires. Patients are asked if it is allowed to consult their medical chart for treatment characteristics and survival length.

8.7 Premature termination of the study

The aim of the study is to investigate a different and possibly safer treatment method than the current standard of care. The study is based on the radiotherapy concept of fractionating the treatment. When the total dose of radiation is divided into several, smaller doses over a period of several days, there are fewer toxic effects on healthy cells. Therefore, the risk of adverse events in the experimental cohort is unlikely to be greater than in the standard cohort and premature termination of the study is not likely.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded in the medical record of the patient.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator shall report serious adverse events to safestereo@haaglandenmc.nl without undue delay after obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required.

Adverse experiences of a serious and unexpected nature, whether or not related to the cerebral radiotherapy, must be reported immediately. Adverse events that are

unexpected, should be reported if there is a possibility that it could be related to the administration of the radiotherapy.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs: epilepsy, deterioration of existing neurologic impairment after the radiotherapy, alopecia, fatigue, headache, and taste disorders.

The sponsor will report the unexpected SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other unexpected SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Patients with brain metastases generally have a poor life expectancy of around 3-12 months. Therefore, a significant proportion of patients is expected to die within the study duration of 1 year after SRT.

Expected SAEs are hospitalization or death by progression of both extracranial and intracranial cancer. Moreover, patients are treated with systemic therapy, and may be hospitalized or die because of complications of the systemic therapy, such as secondary infections. Furthermore, a proportion of patient will have severe neurologic impairment and epilepsy, because of intracranial cancer progression despite radiotherapy. These expected SAEs will be reported every half year in a line listing.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

N/A

9.3 Annual safety report

N/A

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported until end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

The establishment of a Data Safety Monitoring Board or Safety Committee is not deemed necessary for this study. The study aims to investigate a potentially safer treatment method than the current standard of care. It is unlikely that the risk of adverse events will be increased in the experimental cohort compared to the standard cohort. The only difference between the two cohorts is the fractionation schedule. The only difference is expected in the rate of local control and radionecrosis, which constitutes the primary study endpoint.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

Differences in the composite endpoint (either radionecrosis or local failure) at 2 years post-radiotherapy are calculated as a percentage in each cohort. The binomial test will be used to compare the percentage between the two cohorts.
Summary tables for continuous variables will include the following statistics: mean, standard deviation. Summary tables for categorical variables will include: N, proportion.
If the data is normally distributed, the means will be compared using independent samples Student's T-Tests. In case of violation of the normality assumptions, non-parametric tests will be used. Proportions will be compared by using Chi-square testing. Unless otherwise indicated, tests will be 2-sided.

10.2 Secondary study parameter(s)

Secondary study parameters (as listed in paragraph 8.1.2, including facultative endpoints such as HRQoL and neurocognition) will be presented per cohort. Due to the presence of repeated measurements mixed modelling will be used to analyze use of anti-epileptica, dexamethasone and bevacizumab, IADL and to investigate the effect of fSRT on quality of life.

Overall survival (from date of first radiotherapy until death) will be estimated by using Kaplan-Meier methodology. To assess whether there is difference between survival in the groups, the Log-rank test will be used. To investigate the effect of prognostic factors on survival, a Cox regression model will be used. To estimate the cumulative incidence of adverse local events (ALE), a competing risk model with death as a competing risk will be estimated.[18] Fine and Gray's test will be employed to assess the difference between cumulative incidence in the two cohorts.[19] Cause specific hazard Cox model will be employed to investigate the effect of prognostic factors on the cumulative incidence of ALE.
Care will be taken to minimize missing data and to continue to follow up those who withdraw from the study. To account for non-compliance and protocol deviation the analysis will be performed based on the intention to treat concept.
All analyses concerning the competing risk model will be performed in R environment by using the library mstate and cprisk.[20,21] All other analyses will be performed in SPSS version 26.0 (IBM Corp, Armonk, NY).

10.3 Other study parameters

N/A

10.4 Interim analysis

See paragraph 8.7.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The responsible investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki (Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO), as well as the Algemene verordering gegevensbescherming (AVG).
The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP).
The protocol will be approved by the Local, Regional or National Ethics Committees. The treating physician asks the patient to participate. If a patient is interested in the study, the researcher of the participating hospital or physician assistant supplies more detailed information about the study.

11.2 Recruitment and consent

Eligible patients will receive information about this study from the physician on intake, i.e. the radiation oncologist, and will at that time also receive a written patient information and informed consent forms. All patients will be informed about the aims of the study, the possible adverse events, the procedures and possible hazards to which they will be exposed. They will be informed about the strict confidentiality of their data, and that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. Information will be given both spoken and written as in the Patient Information Form. The Patient Informed Consent Statement and the Patient Information text are given as separate documents along with this protocol.

It will be emphasized that the participation is completely voluntary and the patient does not need to give any further explanation for not participating. The patient is allowed to refuse further participation in the protocol whenever they want. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study.

Patients will have at least 2 days or more to consider participation in the study. After 2 days the radiation oncologist will contact the patient and if needed will give the patient more time to reconsider participating in the study. They can contact a physician who is not involved in the study for further independent information about the study protocol. When the patient decides to participate in the study, he will date and sign the informed consent form, sometimes after orally consenting to participation. After the patient has

signed, the physician/researcher or their representative also dates and signs this informed consent. These signing dates are not necessarily on the same day, due to logistical reasons. Planning of treatment can start when oral consent is given. Before any study-related actions take place, the written informed consent must be given to the treating physician. Written informed consent form should be signed and personally dated by the patient as well as the local investigator.

11.3 Objection by minors or incapacitated subjects (if applicable)

Minors are not allowed to participate in this study. Incapacitated subjects are not suited for radiotherapy treatment for brain metastases.

11.4 Benefits and risks assessment, group relatedness

This study is performed on both male and female subjects who are to be treated for brain metastases with radiotherapy. The aim of this study is to assess whether or not fSRT can reduce the incidence of adverse local events compared to SRT in one or three fractions. fSRT and SRT in one or three fractions are globally accepted treatment options for brain metastases, and both treatments will be delivered according to current state of the art. One difference between the two treatment options is that patients receiving fSRT will have to go to the hospital five times to receive the treatment as opposed to once. No side effects are expected in addition to side effects common in daily clinical practice.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 750.000,-- (i.e. seven hundred and fifty thousand Euro) for death or injury for each subject who participates in the research;
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the research;
3. € 7.500.000,-- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the

sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Subjects will not receive any type of special or financial incentives for participating in this study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All anonymized data will be entered into Castor Electronic Data Capture (EDC) system. A code will be attributed to each patient registered in the trial consisting of sequential inclusion number. This code will identify the patient number in the electronic patient dossier. This data needs to be anonymized, because it can be traced back to the individual patient.

The code number must be included on all case report forms. The code will be attributed by the data manager of the radiotherapy department of Haaglanden MC and linked to the non-anonymized data in a list kept by the data manager only. This list is kept in a digitally secure environment of the Haaglanden MC, to which no-one except the data manager and the R&D associate have access.

The non-coded data may only be viewed by the data manager, the responsible physicians and, if necessary, the (national) regulatory authorities. The coded data in Castor EDC can only be viewed by the data manager, the coordinating investigator and principal investigator, as well as by the regulatory institutions.

The duration of the storage of the study data is 15 years. The IGJ (Inspectie Gezondheidszorg en Jeugd) and monitors have permission to check all data and documents.

12.2 Monitoring and Quality Assurance

In accordance with Haaglanden Medical Center guidelines, monitoring is mandatory for all research that is subject to the Medical Research Involving Human Subjects Act (WMO). This will take place 1-2 times a year. And will be arranged by the sponsor.

12.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

First author on papers with results of the study will be JC (Jeroen Crouzen) and last author JZ (Jaap Zindler). The same policy will be applied to side results. Everyone who contributed as well, such as investigators or participating centers, will be considered as co-author. The sequence of co-authorship of participating investigators will be determined by the number of patients included in the study. Persons who contributed in a minor way to a study may be considered for the acknowledgments section. Conflicts will be resolved by the PI and his co-PIs. Results will be published unreservedly regardless of their nature in accordance with the CCMO statement on publication policy.

13. STRUCTURED RISK ANALYSIS

As mentioned in chapter 6 and 7, no medicinal product, food product, medical device or other product is tested in this study. Therefore, this chapter is not applicable.

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