



High-PREcision Radiotherapy of MOtor DEficits due to Metastatic Spinal Cord Compression

Study name: PRE-MODE

A phase 2 multi-center study

Sponsor:

University Hospital Schleswig-Holstein (UKSH)

Study management:

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Version 4.0 (06-05-2019)

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Confidentiality statement

The information contained in this protocol are confidential and may not be communicated to third parties either in spoken or in written form without the explicit permission of the study management. This excludes communication of the required information to the ethics commission responsible or informing the regulatory authorities.

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High-precision radiotherapy of motor deficits due to metastatic spinal cord compression

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It has been confirmed that the protocol, the case report forms and appendices contain all information and regulations necessary for the implementation of the clinical study, and that the study will be conducted and documented in line with this protocol, abiding by the legal regulations and agreements described therein.

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1A Synopsis (English version)

Study title	High-precision radiotherapy of motor deficits due to metastatic spinal cord compression
Study designation	PRE-MODE
Sponsor	University Hospital Schleswig-Holstein, Campus Lübeck
Coordinating Investigator	Prof. Dr. D. Rades, Department of Radiation Oncology, University of Lübeck & University Hospital Schleswig-Holstein, Campus Lübeck, Germany
Study start	January 2017
Study period	30 months: recruitment = 18 months, follow up = 6 months, analyses, reporting and publication = 6 months
Type of protocol	Multinational phase 2 multi-center study (single arm) supplemented by a comparison to a historical, propensity score matched control group (superiority study)
Indication	Motor deficits of the lower extremities due to metastatic spinal cord compression (MSCC)
Rationale	For MSCC, conventional radiotherapy (RT) with 10x3 Gy in 2 weeks results in similar motor function but better local progression-free survival (LPFS) than conventional RT with 5x4 Gy in 1 week. Since patients with MSCC are often significantly impaired, a RT regimen with an overall treatment time of only 1 week would be preferable if it resulted in similar LPFS as 10x3 Gy in 2 weeks. This may be achieved with 5x5 Gy in 1 week, since the equivalent dose in 2 Gy fractions (EQD2) with respect to tumor cell kill of 5x5 Gy and 10x3 Gy are similar. Taking into account the tolerance dose of the spinal cord, 5x5 Gy can be safely administered with high-precision RT such as volumetric modulated arc therapy (VMAT) or stereotactic body radiotherapy (SBRT). This phase 2 study investigates LPFS after high-precision RT with 5x5 Gy in 1 week. The patients of the phase 2 study will be compared for LPFS to a historical control group receiving conventional RT with 5x4 Gy in 1 week. If superiority regarding LPFS is shown for high-precision RT with 5x5 Gy, patients with MSCC would benefit from this regimen, since high LPFS rates can be achieved with an RT regimen of only 1 week (5x5 Gy) instead of 2 weeks (10x3 Gy).
Treatment	Study arm: 5x5 Gy of high-precision RT in 1 week Historical control: 5x4 Gy of conventional RT in 1 week Follow-up directly and at 1, 3 and 6 months following RT
Primary endpoint	LPFS at 6 months following RT
Secondary endpoints	<u>1. Motor function/Ability to walk</u> Assessment directly and at 1, 3 and 6 months following RT

	<p><u>2. Sensory function</u> Assessment directly and at 1, 3 and 6 months following RT</p> <p><u>3. Sphincter dysfunction</u> Assessment directly and at 1, 3 and 6 months following RT</p> <p><u>4. Local progression-free survival</u> Additional evaluation directly and 1 and 3 months following RT</p> <p><u>5. Overall survival</u> Evaluation directly and at 1, 3 and 6 months following RT</p> <p><u>6. Pain</u> Evaluation directly and at 1, 3 and 6 months following RT</p> <p><u>7. Distress (as an indicator of quality of life)</u> Evaluation directly and at 1, 3 and 6 months following RT</p> <p><u>8. Toxicity</u> Evaluation during plus directly, 1, 3 and 6 months following RT</p>
Number of patients	44 patients (phase 2 study)
Inclusion criteria	<ol style="list-style-type: none"> 1. Motor deficits of the lower extremities resulting from MSCC, which have persisted for no longer than 30 days 2. Confirmation of diagnosis by magnetic resonance (MR) imaging (computed tomography (CT) allowed) 3. Age 18 years or older 4. Written informed consent 5. Capacity of the patient to contract
Exclusion criteria	<ol style="list-style-type: none"> 1. Previous RT or surgery of the spinal areas affected MSCC 2. Symptomatic brain tumor or symptomatic brain metastases 3. Metastases of the cervical spine only 4. Other severe neurological disorders 5. Pregnancy, lactation period 6. Indication for decompressive surgery of affected spinal areas
Statistics/Sample size calculation	<p>The primary endpoint of this phase 2 study is to assess high-precision RT with 5x5 Gy in 1 week with respect to 6-month LPFS and to demonstrate that this rate is superior to conventional RT with 5x4 Gy (hypothesis).</p> <p>To ensure with 80% power that – in the phase 2 study- the 95% confidence interval for the true 6-month LPFS rate has a precision of +/-20% a total of 44 patients should be enrolled. For comparison of the prospective study results with historical controls, a propensity score approach will be applied to account for baseline differences between treatment arms to balance covariates and remove bias that may arise due to these confounders. Ten relevant prognostic factors will be included. Assuming that roughly 400 historical controls qualify for this comparison, a power of at least 80% will be ensured assuming that the true 6-month LPFS rate with conventional RT with 5x4 Gy is roughly 67% and a 20% percentage increase is considered as clinically relevant.</p>
End of study	The study is completed when all patients have either died or been followed for at least 6 months and analyses, reporting and publication have been finished, or when the study has been terminated due to other reasons (for example patient safety).

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Flow Chart

	Prior to RT	End of RT	Follow up at 1 month (+/- 2 weeks) following RT	Follow up at 3 months (+/- 2 weeks) following RT	Follow up at 6 months (+/- 2 weeks) following RT
Informed Consent	X				
Medical History/Concomitant Diseases	X				
Prognostic factors	X				
Physical examination	X	X	X	X	X
Inclusion/Exclusion Criteria	X				
Motor Function	X	X	X	X	X
Sensory Function	X	X	X	X	X
Sphincter Dysfunction	X	X	X	X	X
Ambulatory Status	X	X	X	X	X
Pain	X	X	X	X	X
Distress (quality of life)	X	X	X	X	X
Toxicity*	X	X	X	X	X
LPFS		X*	X	X	X
Overall survival		X*	X	X	X

*also during RT

1B Synopsis (German version)

Studientitel	Hochpräzisions-Strahlentherapie bei motorischen Defiziten aufgrund metastatisch bedingter Rückenmarkskompression
Studienbezeichnung	PRE-MODE
Sponsor	Universitätsklinikum Schleswig-Holstein, Campus Lübeck
Studienleiter	Prof. Dr. D. Rades Klinik für Strahlentherapie Universität zu Lübeck & Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Deutschland
Studienstart	Januar 2017
Studiendauer	30 Monate: Rekrutierung = 18 Monate, Follow up = 6 Monate, Analysen, Berichte und Publikation = 6 Monate
Art des Protokolls	Multinationale Phase 2 Multicenter-Studie (einarmig), ergänzt durch den Vergleich mit einer historischen Kontrollgruppe mittels Propensity Score Matching (Überlegenheitsstudie)
Indikation	Motorische Defizite der unteren Extremitäten aufgrund einer metastatisch bedingten Rückenmarkskompression
Rationale	Bei der metastatisch bedingten Rückenmarkskompression (MSCC) führt die konventionelle Bestrahlung mit 10x3 Gy in 2 Wochen zu ähnlicher motorischer Funktion aber zu einem besseren lokalen progressionsfreien Überleben (LPFS) als eine konventionelle Bestrahlung mit 5x4 Gy in 1 Woche. Da Patienten mit MSCC oft deutlich beeinträchtigt sind, wäre eine Strahlentherapie mit einer Gesamtbehandlungszeit von nur einer Woche zu bevorzugen, wenn diese zu einem ähnlichen LPFS führen würde wie 10x3 Gy in 2 Wochen. Dies könnte mit 5x5 Gy in 1 Woche erreicht werden, da die EQD2s von 5x5 Gy und 10x3 Gy hinsichtlich Tumorzellvernichtung ähnlich sind. Wenn man die Toleranzdosis des Rückenmarks berücksichtigt, kann das Regime 5x5 Gy sicher mit einer Hochpräzisions-Strahlentherapie (VMAT oder SBRT) verabreicht werden. Darum untersucht diese Phase 2 Studie die LPFS nach Hochpräzisions-Strahlentherapie mit 5x5 Gy in 1 Woche. Die Patienten/innen der Phase 2 Studie werden hinsichtlich LPFS mit einer historischen Kontrollgruppe verglichen, die eine konventionelle Bestrahlung mit 5x4 Gy in 1 Woche erhalten hat. Kann eine Überlegenheit der Hochpräzisions-Strahlentherapie mit 5x5 Gy gezeigt werden, würden Patienten mit MSCC von diesem Regime profitieren, da sie eine hohe LPFS-Rate mit einem Regime erreichen können, das nur 1 Woche (5x5 Gy) statt 2 Wochen (10x3 Gy) dauert.
Behandlung	Studienarm: Hochpräzisions-Strahlentherapie mit 5x5 Gy in 1 Woche

	<p>Historische Kontrollgruppe:</p> <p>konventionelle Strahlentherapie mit 5x4 Gy in 1 Woche</p> <p>Nachuntersuchungen direkt sowie 1, 3 und 6 Monate nach Strahlentherapie</p>
Primärer Endpunkt	LPFS 6 Monate nach Strahlentherapie
Sekundäre Endpunkte	<p><u>1. Motorische Funktion / Gehfähigkeit</u> Beurteilung direkt sowie 1, 3 und 6 Monate nach Strahlentherapie</p> <p><u>2. Sensibilität</u> Beurteilung direkt sowie 1, 3 und 6 Monate nach Strahlentherapie</p> <p><u>3. Blasen-Mastdarm-Störungen</u> Beurteilung direkt sowie 1, 3 und 6 Monate nach Strahlentherapie</p> <p><u>4. Lokales progressionsfreies Überleben</u> Zusätzliche Beurteilung direkt sowie 1 und 3 Monate nach Strahlentherapie</p> <p><u>5. Gesamtüberleben</u> Beurteilung direkt sowie 1, 3 und 6 Monate nach Strahlentherapie</p> <p><u>6. Schmerz</u> Beurteilung direkt sowie 1, 3 und 6 Monate nach Strahlentherapie</p> <p><u>7. Distress (als Indikator für Lebensqualität)</u> Beurteilung direkt sowie 1, 3 und 6 Monate nach Strahlentherapie</p> <p><u>8. Toxizität</u> Beurteilung während sowie direkt, 1, 3 und 6 Monate nach Strahlentherapie</p>
Anzahl der Patienten	44 Patienten (Phase 2 Studie)
Einschlußkriterien	<ol style="list-style-type: none"> 1. Motorische Defizite der unteren Extremitäten als Ergebnis einer metastatisch bedingten Rückenmarkskompression welche nicht länger als 30 Tage bestanden hat 2. Bestätigung der Diagnose mittels Kernspintomographie (CT genehmigt) 3. Alter 18 Jahre oder älter 4. Schriftliche Einverständniserklärung 5. Geschäftsfähigkeit des Patienten/der Patientin
Ausschlußkriterien	<ol style="list-style-type: none"> 1. Frühere Strahlentherapie oder Operation der von der metastatisch bedingte Rückenmarkskompression betroffenen Wirbelsäulenregionen 2. Symptomatischer Hirntumor oder symptomatische Hirnmetastasen 3. Ausschließlich Metastasen der Halswirbelsäule 4. Andere schwere neurologische Erkrankungen 5. Schwangerschaft, Stillzeit 6. Indikation für eine Dekompressions-Operation der betroffenen Wirbelsäulenregionen
Statistik/Fallzahl-Berechnung	Der primäre Endpunkt dieser Phase 2 Studie beinhaltet die Erfassung der LPFS-Rate nach 6 Monaten nach Hochpräzisions-Strahlentherapie mit 5x5 Gy in 1 Woche sowie den Nachweis, dass diese Rate höher ist als nach konventioneller Strahlentherapie mit 5x4 Gy (Hypothese).

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	<p>Um mit einer statistischen Power von 80% zu gewährleisten, dass in dieser Phase 2 Studie das 95%-Konfidenzintervall für die wahre LPFS-Rate nach 6 Monaten eine Genauigkeit von +/-20% aufweist, müssen 44 Patienten/innen eingeschlossen werden. Für den Vergleich mit der historischen Kontrollgruppe wird ein Propensity Score Matching durchgeführt, um Unterschiede zwischen beiden Gruppen hinsichtlich Patientencharakteristika und Kovariablen auszugleichen und eine durch mögliche Unterschiede resultierende Verzerrung (Bias) zu vermeiden. Zehn relevante Prognosefaktoren werden hierbei berücksichtigt. Unter der Annahme, dass sich ungefähr 400 Patienten/innen für die historische Kontrollgruppe qualifizieren, wird eine statistische Power von 80% erreicht, wobei davon ausgegangen wird, dass die wahre LPFS-Rate 6 Monate nach konventioneller Strahlentherapie mit 5x4 Gy 67% beträgt und eine Verbesserung von absolut 20% als klinisch relevant angesehen wird.</p>
Ende der Studie	<p>Die Studie ist abgeschlossen, wenn alle Patienten entweder verstorben sind oder für wenigstens 6 Monate nachbeobachtet wurden und Analysen, Berichte und die Publikation abgeschlossen sind oder die Studie aus anderen Gründen beendet wurde (zum Beispiel Patientensicherheit).</p>

Ablaufplan

	Vor Strahlentherapie	Am Ende der Strahlentherapie	1 Monat (+/- 2 Wochen) nach Strahlentherapie	3 Monate (+/- 2 Wochen) nach Strahlentherapie	6 Monate (+/- 2 Wochen) nach Strahlentherapie
Einverständniserklärung	X				
Anamnese/Begleiterkrankungen	X				
Prognosefaktoren	X				
Ärztliche Untersuchung	X	X	X	X	X
Ein-/Ausschlusskriterien	X				
Motorische Funktion	X	X	X	X	X
Sensibilität	X	X	X	X	X
Blasen-Mastdarm-Störungen	X	X	X	X	X
Gehfähigkeit	X	X	X	X	X
Schmerz	X	X	X	X	X
Distress (Lebensqualität)	X	X	X	X	X
Toxizität*	X	X	X	X	X
LPFS		X*	X	X	X
Gesamt Überleben		X*	X	X	X

*ebenfalls während der Strahlentherapie

2 List of Abbreviations

AE	adverse event
ASIA	American Spinal Injury Association
GCP	good clinical practice
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEGRO	German Society for Radiation Oncology
ECOG	Eastern Cooperative Oncology Group
EQD2	equivalent dose in 2 Gy fractions
LPFS	local progression-free survival
MR	magnetic resonance
MSCC	metastatic spinal cord compression
OS	overall survival
PR	partial response
PTV	planning target volume
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
RT	radiotherapy
SAE	serious adverse event
SBRT	stereotactic body radiotherapy
UAE	unexpected adverse events
UKSH	University Hospital Schleswig-Holstein
VMAT	volumetric modulated arc therapy

3 Background and Rationale

3.1 Background

Metastatic spinal cord compression (MSCC) occurs in 5-10% of all cancer patients during the course of their disease [1, 2]. Radiotherapy (RT) alone is the most common treatment. However, the most appropriate radiation schedule is still a matter of debate. The survival prognosis of many patients with MSCC is poor measured in months [1-3]. Every radiotherapy session may be associated with discomfort for the often significantly impaired patients in a palliative situation, in particular regarding the transport to the radiotherapy department and the patient's positioning on the treatment couch. Thus, a more patient convenient radiation schedule with a short overall treatment time (short-course radiotherapy such as 5x4 Gy in 1 week) would be preferable if it was as effective as the most commonly used radiation schedule for MSCC, 10x3 Gy in 2 weeks. Both retrospective and prospective studies have shown that 5x4 Gy in 1 week and 10x3 Gy in 2 weeks are similarly effective with respect to their effect on motor function [3, 4].

However, a prospective non-randomized study has demonstrated that longer-course radiotherapy programs such as 10x3 Gy in 2 weeks resulted in better local progression-free survival (LPFS) than short-course programs such as 5x4 Gy in 1 week [5]. LPFS was defined as freedom from progression of motor deficits during RT and freedom from an in-field recurrence of MSCC (i.e. freedom from motor deficits due to a recurrence of MSCC in the previously irradiated parts of the spine) following RT. In that study, which compared longer-course to short-course radiotherapy, the vast majority of the patients in the longer-course RT group had received 10x3 Gy and the vast majority of patients in the short-course RT group 5x4 Gy [5]. The LPFS at 6 months were 86% after longer-course RT and 67% after short-course RT, respectively ($p=0.034$). Local progression of MSCC is a serious situation, since spinal surgery or a second course of radiotherapy in the same area of the spinal cord may not be possible. Therefore, such a progression must be avoided.

The ideal RT schedule for MSCC would be both short and effective in improving LPFS. The biological effect of radiotherapy depends on both the total dose and the dose per fraction [6]. The biologically effective doses of different RT schedules can be compared by calculating the equivalent dose in 2 Gy fractions (EQD2) [7]. The EQD2 with respect to tumor cell kill is 23.3 Gy for 5x4 Gy and 32.5 Gy for 10x3 Gy, respectively. RT of MSCC can be intensified with the use of high-precision techniques such as volumetric modulated arc therapy (VMAT) and stereotactic body radiotherapy (SBRT) considering the tolerance doses of the spinal cord and the vertebral bone [8-11]. The EQD2 of high-precision RT with 5x5 Gy in 1 week is 31.3 Gy, which is similar to the EQD2 of 10x3 Gy (32.5 Gy). Thus, with 5x5 Gy of high-precision RT in 1 week, one can expect similar LPFS as with 10x3 Gy in 2 weeks. The EQD2 of 5x5 Gy for radiation-related myelopathy is 43.8 Gy, which is below the tolerance dose of the spinal cord (45-50 Gy). The EQD2 of 5x5 Gy for damage to the vertebral bone is 41.7 Gy, which is well below the tolerance dose of bone (52 Gy) [9-11]. Therefore, high-precision RT with 5x5 Gy can be considered a safe treatment regarding the risk of radiation myelopathy and damage to the vertebral bone.

In contrast to other countries, decompressive surgery prior to RT has become increasingly popular for MSCC in Germany during the last 10 years, although it has been recommended only for selected patients [12-15]. Thus, the proportion of patients treated with RT alone for MSCC in Germany is decreasing, and a randomized, prospective clinical trial comparing 5x5 Gy of high-precision RT to 5x4 Gy of conventional RT with a sufficiently large sample size will be quite difficult to perform within a reasonable period of time. Therefore, the present study is designed as a single-arm phase 2 study. Subsequently, the patients of the phase 2 study will be compared to a historical control group. Propensity score matching will be performed to balance covariates and remove bias that may arise due to these confounders. Ten potential prognostic factors will be included. This design can be

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considered appropriate to answer the question whether high-precision RT with 5x5 Gy results in significantly better LPFS than 5x4 Gy of conventional RT in patients irradiated for MSCC.

3.2. Rationale

In patients treated with RT alone for MSCC, conventional RT with 10x3 Gy in 2 weeks results in similar motor function but significantly better LPFS than conventional RT with 5x4 Gy in 1 week. Since patients with MSCC are often significantly impaired, a RT regimen with an overall treatment time of only 1 week would be preferable if it resulted in similar LPFS as 10x3 Gy in 2 weeks. This may be achieved with 5x5 Gy in 1 week, since the EQD2 with respect to tumor cell kill of 5x5 Gy and 10x3 Gy are similar. Taking into account the tolerance dose of the spinal cord, 5x5 Gy can be safely administered with high-precision RT such as VMAT (or SBRT). Therefore, the present phase 2 study investigates the LPFS after high-precision RT with 5x5 Gy in 1 week. To demonstrate superiority when compared to conventional RT with 5x4 Gy in 1 week, the patients of the phase 2 study will be compared to a historical control group receiving conventional with 5x4 Gy in 1 week. If superiority regarding LPFS can be shown for high-precision RT with 5x5 Gy, patients with MSCC would benefit from this regimen, since they can achieve high LPFS rates with an RT regimen lasting only 1 week (5x5 Gy) instead of 2 weeks (10x3 Gy). This study aims to make a significant contribution to the most appropriate RT schedule for patients with MSCC.

4 Endpoints

4.1. Primary endpoint

The primary aim of this study is to investigate the LPFS of MSCC after 5x5 Gy of high-precision RT (VMAT = preferred technique, SBRT = allowed for patients with involvement of only one vertebra, if the required constraints [please see 6.2.1] can be met) and to demonstrate that this regimen results in significantly better 6-month LPFS than conventional RT with 5x4 Gy. LPFS is defined as freedom from progression of motor deficits during RT and freedom from an in-field recurrence of MSCC (i.e. freedom from motor deficits due to a recurrence of MSCC in the previously irradiated parts of the spine) following RT. The LPFS rate will be assessed 6 months after the end of RT.

4.2. Criteria for secondary endpoints

In addition, the following endpoints will be evaluated:

1. Motor function/Ability to walk: Assessment directly and at 1, 3 and 6 months after RT
2. Sensory function: Assessment directly and at 1, 3 and 6 months after RT
3. Sphincter dysfunction: Assessment directly and at 1, 3 and 6 months after RT
4. Local progression-free survival: Additional evaluation directly and at 1, 3 and 6 months after RT
5. Overall survival: Evaluation directly and at 1, 3 and 6 months after RT
6. Pain: Evaluation directly and at 1, 3 and 6 months after RT
7. Distress: Evaluation directly and at 1, 3 and 6 months after RT
8. Toxicity: Evaluation during RT, and directly, 1, 3 and 6 months after RT

5 Study Design and Patient Selection

5.1 General design and duration

This is a single-arm study, which will investigate the effect of high-precision RT with 5x5 Gy on LPFS in patients irradiated for MSCC.

The recruitment of all 44 patients (40 patients + 10% for potential drop-outs) should be completed within 18 months. The follow-up period will be 6 months. Another 6 months are required for analyses, reporting and publication. This equals a total running time for the study of 30 months.

In accordance with a previous study assessing local control of MSCC, the following patient characteristics will be recorded to allow adequate comparison with the historical, propensity-score matched control group [16]:

- Age (2 groups, depending on median age)
- Gender
- Type of primary tumor (breast cancer vs. prostate cancer vs. myeloma/lymphoma vs. lung cancer vs. other tumors)
- Interval from tumor diagnosis to MSCC (≤ 15 months vs. > 15 months)
- Number of involved vertebrae (1-2 vs. ≥ 3)
- Other bone metastases at the time of RT (no vs. yes)
- Visceral metastases at the time of RT (no vs. yes)
- Time developing motor deficits prior to RT (1-7 days vs. 8-14 days vs. > 14 days)
- Ambulatory status prior to RT (no vs. yes)
- Eastern Cooperative Oncology Group (ECOG) performance score (1-2 vs. 3-4)

5.2 Patient selection

5.2.1 General prerequisites

Patients have to be adequately informed about their diagnosis and about the nature, significance and scope of the study. Patients may only be included after completing the pre-therapy clarification and on fulfilment of all inclusion criteria and on non-fulfilment of all exclusion criteria. Prior to inclusion in the study, it should be clear that the patient is no clear candidate for decompressive surgery of the parts of the spinal cord involved by MSCC.

5.2.2 Inclusion and exclusion criteria

Inclusion criteria	<ol style="list-style-type: none"> 1. Motor deficits of the lower extremities resulting from MSCC*, which have persisted for no longer than 30 days 2. Confirmation of diagnosis by MR-imaging (CT allowed) 3. Age 18 years or older 4. Written informed consent 5. Capacity of the patient to contract
Exclusion criteria	<ol style="list-style-type: none"> 1. Previous RT or surgery of the spinal areas affected MSCC 2. Symptomatic brain tumor or symptomatic brain metastases 3. Metastases of the cervical spine only 4. Other severe neurological disorders 5. Pregnancy, Lactation 6. Indication for decompressive surgery of affected spinal areas

*MSCC may affect single or multiple spinal sites

5.2.3 Termination criteria for individual patients

The patient may terminate participation in the study at any time and without giving any reasons. Otherwise, the reasons for terminating participation in the study are the same as those for individually breaking off treatment with radiotherapy.

- Serious adverse event (SAE), which necessitates termination of treatment
- Unacceptable toxicities
- Pregnancy

Date and reason for termination of treatment have to be documented, if indicated by the patient.

5.2.4 Termination criteria for the study in general

The clinical study can be terminated by the coordinating investigator if new findings and/or risks should come to light that necessitate a reassessment of the risk/benefit ratio and which results in a negative result.

5.2.5 Definition of the end of the study

The study is completed when all patients have either died or been followed up for at least 6 months, or the study has been terminated.

The patient will continue to receive treatment at the clinic in question after the 6-month follow-up period, or the premature termination of the study for the patient.

6 Treatment

6.1 Patient registration

The patients were assigned 2 code numbers, the number of the contributing center plus a patient ID number starting with 001 and chronologically ongoing.

Coordination and supervision of the inclusion of the patients will be performed by the Department of Radiation Oncology of the University of Lübeck, Germany.

Patients can be registered by e-mail (dirk.rades@uksh.de) or by fax (0049-451-500 45404).

6.2 Treatment

6.2.1 Radiotherapy

Radiotherapy is administered as high-precision radiotherapy with 25.0 Gy in 1 week, i.e. with 5.0 Gy per fraction on 5 days per week (representing an EQD2 of 43.8 Gy for radiation myelopathy) [6, 7]. An EQD2 of 45 Gy is estimated to be associated with a risk of radiation-related myelopathy of 0.03% and is therefore considered safe [8]. VMAT (6-10 MeV photon beams) is the preferred technique. SBRT is allowed for patients with involvement of only one vertebra, if the following constraints can be met. The clinical target volume (CTV) includes the vertebral and soft tissue tumor as seen on the planning computed tomography and diagnostic MR-imaging, the spinal canal, the width of the involved vertebrae, and half a vertebra above and below those vertebrae involved by MSCC. The planning target volume (PTV) should include the CTV plus 0.8 cm and should be covered by the 95%-isodose. The maximum relative dose allowed to the spinal cord is 101.5% of the prescribed dose (representing an EQD2 of 44.9 Gy for radiation myelopathy). This maximum dose is estimated to be associated with a risk of radiation-related of <0.03% and is, therefore, also considered safe [8]. Both the EQD2 of the prescribed dose (41.7 Gy) and the EQD2 of the maximum dose (43.8 Gy) are well below the tolerance dose of bone [9-11]. In accordance with the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) data, the mean doses (EQD2) for esophagus, heart and lung must be <34 Gy, <26 Gy and ≤ 7 Gy, respectively [9]. Taking into account a radiation regimen of five fractions, the corresponding mean doses per fraction are 4.5 Gy, 3.8 Gy and 1.54 Gy, respectively [6, 7]. MSCC may affect single or multiple spinal sites. All sites need to be treated with high-precision RT following the dose prescriptions and constraints given above.

6.2.2. Concomitant treatment

It is recommended that the patients receive concomitant dexamethasone during the period of radiotherapy if indicated [1, 2]. [Regarding dose, type and duration of treatment, contraindications, side effects, pharmacological characteristics and pharmaceutical details about dexamethasone, please see relevant product information in the patient information leaflet included in the drug package.]

6.2.3. Possible side effects of high-precision RT

High-precision RT in the thoracic spinal area may be associated with nausea and vomiting, whereas RT in the lumbar spine may be associated with diarrhea. In case of grade 3 toxicity according to Common Terminology Criteria for Adverse Events (CTCAE), RT may be delayed for a maximum of 7 days. If the symptoms persist, RT will be terminated. If RT has to be terminated, the head of the clinical study has to be informed.

7 Safety Management

7.1 Definitions

7.1.1 Adverse events

An adverse event (AE) is any event experienced by a patient or subject of a clinical study, which does not necessarily have a causal relationship to treatment. An AE can therefore be any adverse or inadvertent occurrence (including notable laboratory findings), symptom or illness that occurs in the treatment period, no matter whether there is a causal relationship or not. Existing illnesses that deteriorate during the study should be reported as AE. They may lead to SAEs if they fulfil the criteria below.

Events covered by the documentation for concomitant diseases, the skin status or the radiation related acute toxicity grade (CTCAE v4.03) Grade 1 do not have to be additionally documented as adverse events. If an additional concomitant disease appears after the start of the study an adverse event form has to be completed.

7.1.2 Unexpected adverse events

Unexpected adverse events (UAEs) are those whose type, frequency and degree of severity are not expected based on current knowledge.

7.1.3. Serious adverse events

Serious adverse events (SAEs) are those which fulfil one of the following criteria at any dose level:

- Lethal (resulting in death) event (Note: death is the result, not the event itself)
- Life-threatening event (Note: the term “life-threatening” refers to an event in which the patient was in danger of death at the time the event occurred but not to an event that may have resulted in death had it been more serious.)
- Patient had to be admitted to hospital or his/her hospital stay had to be extended as a result of the event
- Any event leading to permanent or significant disability.
- Birth defects or malformations
- Any medically significant intervention in order to prevent one of the outcomes mentioned above

Hospitalization should be defined as such that the hospitalization was necessary in order to treat the AE. Hospital stay as part of the treatment outlined in the protocol or as a result of a planned, elective operation is not classified as SAE. Likewise, an elective hospitalization to facilitate the study process does not count as SAE.

7.2 Assessment and documentation of adverse events

The severity of AEs should be assessed for clinical effects according to the following scale:

1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening and 5 = fatal.

The following scale should be used to describe the likelihood that the event was caused by the study treatment: **1 = certain/definitely caused by study treatment; 2 = probable; 3 = possible; 4 = unlikely; 5 = not related; and 9 = not assessable.**

7.3 Reporting of adverse events

SAEs and UAEs must be reported within 24 hours after their detection/onset by fax to the address below (see separate document attached to the case report form):

Prof. Dr. Dirk Rades

*Klinik für Strahlentherapie, Universität zu Lübeck
Ratzeburger Allee 160; 23538 Lübeck, Germany*

Tel.: +49 (0)451 500 45400

Fax: +49 (0)451 500 45404

Email: dirk.rades@uksh.de

8 Assessments

8.1 Summary of assessments

The following assessments will be performed as part of this study:

	Prior to RT	End of RT	Follow up at 1 month (+/- 2 weeks) following RT	Follow up at 3 months (+/- 2 weeks) following RT	Follow up at 6 months (+/- 2 weeks) following RT
Informed Consent	X				
Medical History/Concomitant Diseases	X				
Prognostic factors	X				
Physical examination	X	X	X	X	X
Inclusion/Exclusion Criteria	X				
Motor Function	X	X	X	X	X
Sensory Function	X	X	X	X	X
Sphincter Dysfunction	X	X	X	X	X
Ambulatory Status	X	X	X	X	X
Pain	X	X	X	X	X
Distress (quality of life)	X	X	X	X	X
Toxicity*	X	X	X	X	X
LPFS		X*	X	X	X
Overall Survival		X*	X	X	X

*also during RT

8.2 Data assessment and prior to start of high-precision RT

The following parameters will be recorded at the start of the study:

Date of birth (age), gender, time between onset of motor deficits and start of RT, type of imaging used for diagnosis of MSCC, interval between initial tumor diagnosis and MSCC, dexamethasone treatment, surgical consultation, localization and number of involved vertebrae, type of primary tumor / histology, presence of other bone metastases or visceral metastases prior to RT, performance status (ECOG-PS, **Appendix IV**), motor function / ambulatory status (according to the modified Tomita scale [17], sensory function, sphincter dysfunction, pain score, and distress (as an indicator of quality of life) score [18] (**Appendix III**).

8.3 Assessments with respect to primary and secondary endpoints

The following parameters will be assessed continuously throughout the course of the study:

8.3.1 Local progression-free survival

Local progression-free survival (LPFS) is defined as freedom from progression of motor deficits during RT and freedom from an in-field recurrence of MSCC (i.e. freedom from motor deficits due to a recurrence of MSCC in the previously irradiated parts of the spine) following RT [5]. LPFS time will be calculated from the last day of the radiotherapy treatment. LPFS will be regularly assessed clinically (physical examination) at 1, 3 and 6 months following RT. In case of a suspected recurrence of MSCC (i.e. progression of existing or development of new motor deficits), a spinal MR-imaging will be performed to confirm or exclude an in-field recurrence of MSCC. In case of progression of existing or development of new motor deficits between two regular follow-up visits, spinal MR-imaging will be performed at any time. The number of MR-imaging sessions is minimized to clinically relevant situations, since patients with MSCC are often quite debilitated. Thus, diagnostic procedures, which may be burdensome for the patients, may not be performed for study purposes alone. The medical history/concomitant diseases will be assessed once at baseline. Newly developed diseases have to be documented as adverse events.

8.3.2 Motor function / Ability to walk

Motor function will be evaluated using the following scale according to Tomita et al. [17] prior to RT, at the end of RT, and at 1, 3 and 6 months following RT. Improvement or deterioration of motor function was defined as a change of at least 1 point.

- 0 = Normal strength
- 1 = Ambulatory without aid
- 2 = Ambulatory with aid
- 3 = Not ambulatory
- 4 = Complete paraplegia

Motor function will additionally be evaluated separately for each leg using the following scale in reference to the American Spinal Injury Association (ASIA) classification [19] resulting in total points of 0 to 14. Improvement or deterioration of motor function was defined as a change of at least two points.

- 0 = Complete paraplegia
- 1 = Palpable or visible muscle contractions
- 2 = Active movement, without gravity
- 3 = Active movement, against gravity
- 4 = Active movement, against mild resistance
- 5 = Active movement, against intermediate resistance
- 6 = Active movement, against strong resistance
- 7 = Normal strength

8.3.3 Sensory function / Sphincter dysfunction

Sensory function:

Sensory function will be evaluated using the following scale, modified in accordance to the ASIA classification [19].

0 = Absent

1 = Impaired

2 = Normal

9 = Cannot be assessed

Sphincter dysfunction:

Sphincter dysfunction will be evaluated as yes vs. no.

8.3.4 Overall survival

Overall survival (OS) time will be calculated for each patient from the last day of radiotherapy up to 6 months following RT. Patients will be followed up until death or for at least 6 months.

8.3.5 Pain

Vertebral pain will be evaluated with a numeric rating scale (self-assessment by patients) from 0 to 10 points (0=no pain, 10=worst pain) prior to RT and directly, 1, 3 and 6 months following RT. Improvement by two points is rated partial response (PR), 0 points complete response (CR). Pain will be assessed prior to RT and directly and 1, 3 and 6 months following RT.

8.3.6 Distress (as an indicator of quality of life)

Distress will be assessed using the distress thermometer (**Appendix III**) [18]. Patients can rate their distress between 0 and 10 (0 = no distress, 10 = extreme distress). Distress will be assessed prior to RT and directly and 1, 3 and 6 months following RT. Improvement of distress was defined as a decrease by at least two points compared to the distress-score prior to RT (baseline).

8.3.7 Toxicity

Toxicity will be assessed according to CTCAE 4.03 during RT, directly after RT and at 1, 3 and 6 months following RT [20]. If radiation myelopathy is suspected (i.e. deterioration according to the modified ASIA scale [19]), spinal MR-imaging will be performed.

9 Comparisons to Historical Control Group

The patients of this study who received high-precision RT with 5x5 Gy for MSCC will be matched to historical control group treated with 5x4 Gy of conventional RT between 2001 and 2016. This data set consists of 680 patients.

The patients of the control group are part of an already existing anonymized database. To be eligible for control group, patients fulfilling the same inclusion criteria and exclusion criteria as defined in the prospective phase II study are considered. Furthermore, to be consistent with efficacy analysis of phase II study, patients of the historical control group must have received at least 80% of the planned RT dose. This will lead to more than 600 patients qualifying for the comparison with the prospectively collected phase 2 data.

For comparison purposes, a propensity score approach will be applied to account for baseline differences between treatment arms to balance covariates and remove bias that may arise due to these confounders. A propensity score is a conditional probability of assignment to a particular treatment given a number of baseline covariates. Except for unmeasured potential confounding factors, patients having the same propensity score but assigned to different treatments will tend to have the same (or nearly the same) distributions on their background covariates and thus are considered to be similar to random assignment of treatments. To estimate the odds of receiving a specific radiotherapy a non-parsimonious multivariable logistic regression model will be estimated. Covariates to be included in the model will be the following ten prognostic factors [16]:

- Age (2 groups, depending on median age)
- Gender
- Type of primary tumor (breast cancer vs. prostate cancer vs. myeloma/lymphoma vs. lung cancer vs. other tumors)
- Interval from tumor diagnosis to MSCC (≤ 15 vs. > 15 months)
- Number of involved vertebrae (1-2 vs. ≥ 3)
- Other bone metastases at the time of RT (no vs. yes)
- Visceral metastases at the time of RT (no vs. yes)
- Time developing motor deficits prior to RT (1-7 days vs. 8-14 days vs. > 14 days)
- Ambulatory status prior to RT (no vs. yes)
- Eastern Cooperative Oncology Group (ECOG) performance score (1-2 vs. 3-4)

Once estimated, adjustment will be accomplished by stratifying the data set on the propensity score, calculating the treatment effect within strata and then pooling the strata-specific treatment effect estimates.

Rosenbaum and Rubin have shown that perfect stratification based on the propensity score will produce strata where the average treatment effect within strata is an unbiased estimate of the true treatment effect [21]. Due to the differences in total sample size between the phase II study and the historical data set, the stratum boundaries will be based on the values of the propensity score for the phase II data alone.

One approach is to use quintiles of the estimated propensity scores to determine the cut-offs for the different strata. The success of propensity score approach will be examined by examining the covariate imbalance between treatment arms before and after adjusting for their propensity quintile. This will be done using a two-way analysis of variance model which includes main effects for propensity score quintile (codes as a class variable with 4 degrees of freedom) and treatment arm. The F-statistic for treatment arm after adjustment for propensity score quintiles will then be compared with the F-statistics for treatment arm prior to adjustment for propensity score quintile to determine whether balance was achieved after stratification based on the propensity score.

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Furthermore, the propensity score will be evaluated for good calibration as measured by the propensity score predicted and observed proportions of treatment group arms within quintiles of the propensity score. To investigate whether propensity scores removed bias due to differences in covariates between studies and to compare binary study endpoints after stratification of patients by propensity scores Cochran-Mantel-Haenszel tests were performed.

Comparisons between the patients of the phase 2 study and the historical control group will be performed for LPFS, OS, motor function and ambulatory status.

10 Statistics

10.1 Sample size calculation

The primary goal of this study is to assess high-precision RT with 5x5 Gy in 1 week with respect to 6-month LPFS and to demonstrate that this rate is superior to conventional RT with 5x4 Gy with respect to LPFS of MSCC (hypothesis).

With respect to tumor cell kill, the equivalent dose in 2 Gy fractions (EQD2) of 5x5 Gy is similar to the EQD2 of 10x3 Gy (31.3 Gy vs. 32.5 Gy) and higher than the EQD2 of 5x4 Gy (23.3 Gy) . In a previous prospective non-randomized study, the 6-month LPFS rates were 86% after longer-course RT and 67% after short-course RT, respectively ($p=0.034$). In that study, 95 of 117 patients (81%) in the longer-course RT group had received 10x3 Gy, and 91 of 114 patients (80%) in the short-course RT group had received 5x4 Gy. Thus, assuming - for the present study – that conventional RT with 5x4 Gy in fact results in a 6-month LPFS rate of 67%, an increase by roughly 20 percentage point is considered to be clinically minimal relevant and even appears to be realistic when applying high-precision RT with 5x5 Gy.

The sample size is chosen to firstly obtain prospective phase 2 data that can be interpreted on its own and to secondly allow for comparison with historical data:

- A sample size of at least 40 eligible patients is needed to estimate the probability of LPFS at 6 month with adequate precision, based on the following assumptions:
 - 6-month LPFS can be assumed to be 87%
 - 6-month LPFS is to be estimated with a precision of plus/minus 20 percentage points expressed as the half length of the associated two-sided confidence interval with a confidence coefficient of 95%.
 - The power -i.e. the probability to obtain this precision, should be at least 80%
 - Clopper-Pearson confidence limits are used as the approach for sample size.

Assuming that roughly 10% of enrolled patients will not be eligible for efficacy analysis due to early lost-to-follow-up or due to premature discontinuation of high-precision RT, a total of 44 patients should be enrolled in the prospective part of the trial.

- As described in section 8, the confirmatory study aim is to compare the prospectively collected phase II data with a historical, propensity-score matched cohort collected up to the time of data analysis. Assuming for simplicity and conservative power calculation that this comparison could be conducted with a simple Pearson-Chi-Square test using a two-sided significance level of 5% (10%), a power of 79% (86%) is reached, if 40 patients are treated with high-precision RT and roughly 400 patients of the historical control group qualify for Propensity-Score adjusted comparison and assuming that the expected 6-month LPFS are 87% and 67%, respectively. Taking into account that the more sophisticated propensity-score adjusted statistical analysis (see section 8) will increase statistical power, the power for treatment arm comparison reached

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with 40 eligible patients in the prospective phase 2 part of the study can be assumed to be at least 80%.

10.2. Statistical analyses

10.2.1 Primary endpoint:

The primary endpoint (LPFS of MSCC) will be evaluated based on the sample size calculations described above. The evaluation will be performed in those patients, who are available for assessment of the primary endpoint and have received at least 80% of the planned RT dose. Due to the open nature of the study, a blind data review is not necessary. The safety population includes all patients who have received at least 1 fraction of high-precision RT.

LPFS is defined as freedom from progression of motor deficits during RT and freedom from an in-field recurrence of MSCC (i.e. freedom from motor deficits due to a recurrence of MSCC in the previously irradiated parts of the spine) following RT [5]. Deterioration of motor deficits during RT will be counted as LPFS of 0 months. Freedom from an in-field recurrence following RT will be referenced from the last day of RT. To investigate clinically important, sustainable effects of precision radiotherapy and avoid over-evaluation of early temporal shifts without any longer term relevance, study design and analysis focuses on binary endpoints evaluated at 6-months rather than time-to-event analyses.

10.2.2 Secondary endpoints:

Secondary endpoints:

An improvement or deterioration of the motor function will be defined as a change of at least 1 point on a 5-point scale [17]. Effect of RT on motor function and post-RT ambulatory rates will be evaluated directly after RT and at 1, 3 and 6 months following RT in those patients who are alive and available for assessment. To investigate whether propensity scores removed bias due to differences in covariates between studies and to compare binary study endpoints after stratification of patients by propensity scores Cochran-Mantel-Haenszel tests were performed. P-values of <0.05 are considered significant.

Overall survival (OS) will be counted from the last day of RT. To investigate clinically important, sustainable effects of precision radiotherapy and avoid over-evaluation of early temporal shifts without any longer term relevance, study design and analysis focuses on binary endpoints evaluated at 6-months rather than time-to-event analyses. The analysis of OS will be conducted in the intent-to-treat population.

Data regarding sensory deficits, sphincter dysfunction, pain, distress and toxicity will only be assessed in the phase 2 study.

11 Ethical and Legal Principles

The examinations to be carried out as part of this study are all considered standard procedures. There are no additional laboratory tests, X-rays or other examinations that could be potentially burdensome for the patient.

11.1 Ethics committee vote

The study protocol will be submitted to the ethics committee responsible. The positive vote of the ethics committee has to be communicated to the coordinating investigator. (**Appendix V**)

11.2 Official registration

Because the study includes radiotherapy, an application must be submitted to the Expert Committee of the German Society for Radiation Oncology (DEGRO) and, if required by the Expert Committee, additionally to the Bundesamt für Strahlenschutz (German Federal Office for Radiation Protection).

11.3 Insurance

Insurance for patients in Germany participating in this study is covered by:

Allianz Versicherungs-Aktiengesellschaft, 10900 Berlin, Germany (insurance policy no. AS-9100160845). (Appendix VI)

11.4 Patient information and informed consent

Patient information and informed consent will be submitted along with the study protocol for evaluation by the ethics committee responsible. Before inclusion in the study, each patient will be fully informed about the content and procedure of the study (**Appendix I**).

If the potential study patient has received the necessary information and if the investigator is sure that the patient has understood this information, the patient will be asked to give his/her consent by signature (**Appendix II**).

The patient will receive a copy of the patient information and the signed informed consent form. The investigator must also inform the patient that he/she has the right to withdraw consent to participate in the study at any time and without having to give any reasons. Patients must be informed that the data collected as part of the study will be documented anonymously and will then be forwarded for scientific evaluation. This is also the appropriate point to indicate the patient consent to data protection.

11.5 Declaration of Helsinki

The study will be conducted in accordance with the principles laid out in the Declaration of Helsinki and in accordance with the principles of good clinical practice (GCP).

11.6 Data protection

Data will be collected in accordance with the regulations set out in the Data Protection Act. All findings from the clinical study will be stored on electronic data storage devices and treated with utmost confidentiality. Organization measures have been taken in order to prevent the data from being communicated to unauthorized persons. Patients will only be identified via their individual patient numbers throughout the entire documentation and evaluation phase and their full name will not be used.

12 Data Management

12.1 Patient identification list

All data relating to patients will be recorded in a pseudonymous way. Each patient will be identifiable only by the unique patient number. A patient identification list will only be kept in the relevant study centers and will not be forwarded to the sponsor.

12.2 Documentation forms

Data collection will be done using the case report forms (CRFs) (**separate document**).

The data documentation forms have to be filled in using a ballpoint pen. Do not use fountain pens or pencils. Corrections have to be made as follows: cross the error out once with a straight line, enter the correct information next to it and note the date and/or reason for correction. Comments have to be made if data fields cannot be filled in because of missing information.

The forms should be filled in as soon as possible and should be submitted to the principal investigator of the contributing center for review, signed, dated and forwarded to the coordinating investigator. After review and clarifying potential questions, the coordinating investigator will forward the forms to the study management office (“Zentrum für Klinische Studien” at the University of Lübeck).

12.3 Monitoring

Monitoring will be performed by the “Zentrum für Klinische Studien” at the University of Lübeck. The frequency of monitoring visits per site will be defined depending on the recruitment rate and the quality of data.

12.4 Direct access to source data / documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

12.5 Storage of study documents

The central study documents, including the documentation sheets, will be kept at the sponsor for a minimum of 10 years after the final report according to the current GCP guidelines. The principle investigator of each study center will keep all administrative documents (written correspondence with the ethics committee, regulatory authorities, study management office, coordinating investigator/study coordinating office), the patient identification list, the signed informed consent forms, copies of the documentation sheets and the general study documentation (protocol, amendments) of his/her center for the above mentioned period. Original patient data (patient files) have also to be kept for the length of time stipulated for the study centres, but not for less than 10 years.

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PRE-MODE

Appendix I Patient information

Address of the Center (Stamp):

Name of the Physician:

phone:

phone:

Patient information regarding the clinical study

High-precision radiotherapy of motor deficits due to metastatic spinal cord compression

Study designation: PRE-MODE

Sponsor of the clinical study:
University Hospital Schleswig-Holstein, Campus Luebeck

Coordinating investigator: Prof. Dr. med. Dirk Rades

Patient-No.: |__|__|__|

Patient-Initials: |__|__|

Please read this information sheet carefully, before making a decision. This sheet includes important information regarding this clinical study. Your treating physician will directly talk to you about this study. Please ask your physician, if you do not understand parts of this information sheet or if you have additional questions.

Dear Patient,

We would like to ask you to read this information sheet very carefully. It contains important information about this clinical study. Your treating physician will answer any questions.

You have been diagnosed with malignant metastases of the vertebral bodies, which are to be treated with radiotherapy. For this reason, you are invited to take part in the study:

High-precision radiotherapy of motor deficits due to metastatic spinal cord compression.

This study investigates high-precision radiotherapy as a treatment of motor deficits (weakness) of the legs caused by compression of the spinal cord by vertebral metastases (metastatic spinal cord compression). The treatment includes 5 radiotherapy sessions (1 session per day) and takes 1 week.

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It is supposed that high-precision radiotherapy with 5 fractions (with a dose of 5 Gy each) can reduce the risk of recurrent motor deficits due to metastatic spinal cord compression in the irradiated parts of the spine more effectively than conventional radiotherapy with 5 (with a dose of 4 Gy each) fractions. High-precision radiotherapy allows the delivery of a higher dose to the vertebral metastases causing metastatic spinal cord compression due to better sparing of the spinal cord when compared to conventional radiotherapy. The higher dose is supposed to result in better control of the metastases.

Study procedure

If you give your consent to take part in this clinical study, you will have to undergo a physical examination before the start of the study. In addition, you will also be asked about any pain you experience as well as about your quality of life. Before the start of your radiotherapy, a computed tomography required for treatment planning will be performed. You will receive such a computed tomography also if you do not take part in this study. After completion of treatment planning, you will receive your radiation treatment, which consists of 5 sessions (fractions) of high-precision radiotherapy, generally administered on 5 consecutive working days.

You will have to undergo a physical examination and answer questions about any pain and about your quality of life directly after the end of your radiotherapy treatment and at 1 month, at 3 months and at 6 months following radiotherapy. These procedures are necessary to evaluate the course of your disease and your state of health.

Aims of the clinical study

The major goal of this clinical study is to investigate to which extent high-precision radiotherapy with modern techniques can prevent progression or recurrence of motor deficits (weakness) of the legs following radiotherapy. In addition, it will be evaluated to which extent radiotherapy can lead to improvement of motor function, ambulatory status, sensory function and sphincter dysfunction, to pain relief and to improvement in quality of life, side effects and overall survival.

Structure of the clinical study

A total of 44 patients from Germany, Denmark and Spain are planned to take part in the clinical study, who will receive modern high-precision radiotherapy treatment for the metastases on their vertebral bodies.

The coordinating investigator of this study is:

Prof. Dr. med. Dirk Rades

Klinik für Strahlentherapie

Universitätsklinikum Schleswig-Holstein, Campus Lübeck

Ratzeburger Allee 160

23538 Lübeck

phone: 0049 (0) 451 500-45400/-45401

Your treating radiation oncologist will inform you about the radiotherapy in detail.

Your responsibilities during the study

For a successful treatment, it is important that you keep the appointments during the treatment and the follow up period and that you follow the instructions of your study physicians. Concurrent

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participation in another study is only allowed in agreement with your study physicians. You may be excluded from the study due to medical reasons. The data collected within this study will be further analyzed; no additional data will be collected.

If you experience ambiguous symptoms during the course of this clinical study, you have to inform your treating physicians. In case of severe symptoms, you have to inform your treating physicians immediately, if necessary by phone (see contact data on the first page of this information sheet). This is mandatory to allow your physicians to identify the measures that are most appropriate for you in this situation.

Potential side effects of treatment

Each type of radiotherapy may cause skin reactions (erythema) and fatigue. Radiotherapy in the region of the thoracic spine may cause nausea and vomiting, while radiotherapy in the region of the lumbar spine may cause diarrhea. As a late effect, radiotherapy may possibly lead to damage to the spinal cord with neurologic deficits. However, the dose administered in this study does not exceed the tolerance dose of the spinal cord such as sensory disorders and motor weakness of the legs. The radiation dose administered within this study will not exceed the tolerance dose of the spinal cord. According to the literature, the risk of radiation-related spinal cord damage is estimated to be less than 0.03%.

Radiotherapy for metastatic spinal cord compression often requires concomitant administration of cortisone (mostly dexamethasone). Therefore, it is likely that you will receive daily cortisone treatment during the period of radiotherapy. Because cortisone can lead to gastritis and may even cause gastric ulcers, you will also receive medication to protect the stomach. In very rare cases, you may experience temporary psychological changes. Your treating physicians will take into account your individual situation, possible risks and side effects when defining your dose of cortisone. For potential side effects, please see also the patient information leaflet included in the drug package.

Alternative treatment options

Radiotherapy alone is the most frequently used treatment option in case of metastatic spinal cord compression. Different treatment concepts are available.

The two most frequently used concepts consist of 5 sessions with a dose of 4 Gy each (comparator group in the course of this clinical study) or 10 sessions with a dose of 3 Gy each. The effect of 10 sessions with 3 Gy each directed to the metastases equates the effect of 5 sessions with 5 Gy each (concept of this clinical study).

For selected patients an additional surgery conducted before radiotherapy might be an option. It will be clarified with a neurosurgeon or an orthopedic surgeon if you are eligible for surgery before start of treatment.

In single cases (extremely bad prognosis) a relinquishment of radiotherapy might be considered and the treatment might be reduced to palliative care.

Voluntary participation

You will be informed in detail about this study by your physician and will have to give your written consent before taking part. Your participation in this study is voluntary, and you can withdraw your consent at any time and without giving any reason. This will not result in any disadvantage for you. If you prematurely terminate your participation in this study, it is very important for you and for the study that you come to a final examination.

During the clinical study you have to inform your study physician about any medical treatment you receive outside this study.

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Your treating physicians will answer any other questions you may have regarding the examinations you will undergo as part of this study and about the results of the findings regarding your treatment and any consequences.

Premature termination of the study

Under certain circumstances, it may be possible that your study physician or the sponsor decides to prematurely terminate your participation in the study and that you will have no influence on this decision. Potential reasons for premature termination are:

- Your further participation in the study is no longer medically acceptable.
- The entire study will be terminated.
- You are not suitable for participating in the study due to the results of the initial clinical examination.

Insurance

A specific clinical studies insurance policy will be taken out for you during this clinical study. During this clinical study, you may only receive additional medical treatment with the agreement of your study physician. This does not apply in a medical emergency but the study physician has to be informed immediately of any emergency medical treatment.

Any detriment to your health that may have resulted from this clinical study has to be communicated to the insurance without delay:

**Allianz Versicherungs-AG, 10900 Berlin, Germany
insurance policy no. AS-9100160845.**

In case the patient dies in the course of treatment, the legal successor of the patient should inform the insurance company by fax within 48 hours.

You are obliged to fulfil all measures that serve to explain the cause or extent of any damage suffered or its reduction. In case you not fulfil this obligation on purpose or out of gross negligence, the insurance policy is no longer valid. In the case of gross negligence, the obligation to perform still exists as long as the breach does not influence the insurance claim or the extent of the same. We would like to point out that no insurance for commuting accidents has been taken.

Data protection:

During the clinical study, medical findings and personal information will be recorded at the center in your personal patient file or saved in electronic form. The key data for the clinical study will additionally be saved in pseudonymous form, evaluated and possibly communicated to third parties if relevant. Pseudonymous means that neither your name nor your initials will be used, but instead a numerical code. The data will be protected against unauthorized access. This data will only be decrypted under the conditions stipulated by law. The data may be forwarded under conditions that ensure their confidentiality to health authorities or other institutions of the sponsor. Due to legal regulations, certain authorized persons have the right to inspect your personal data. These persons include monitors, auditors and other representatives of the sponsor. The inspection will be performed only as a part of their tasks as regulated by law,

namely for data review. Depending on national law, you might have the right to inspect and correct your stored personal data. You might also have the power of veto regarding the transfer of data protected by professional secrecy that could be used and processed within this study.

You may claim these rights from the physician, who guides you within this study and knows your identity. The transfer and storage of your data in pseudonymous form is mandatory for this clinical study. The results of this study in anonymous form are planned be published as a scientific paper and/or presented at scientific meetings.

Further notes

If you are ready to give your informed consent to participate in this study, please sign the informed consent form below to confirm the knowledge of the consequences of the study.

Appendix II Informed consent form

Header/Stamp of the treating clinic

Informed consent form for participation in the clinical study

High-precision radiotherapy of motor deficits

due to metastatic spinal cord compression

Sponsor of the clinical study

University Hospital Schleswig-Holstein, Campus Lübeck

Coordinating Investigator: Prof. Dr. med. Dirk Rades

Patient: Full Name: _____

Date of birth: _____

Physician: Full Name: _____

I have been informed by the above mentioned physician in detail about the nature, extent and significance of this study, including the study aim and duration, requirements and possible side effects, my rights and obligations, insurance coverage and voluntariness of participation. I was assured that the informing was complete. I have received, read and understood the patient information and a copy of the informed consent form. The questions I had with respect to these have been answered adequately and completely. I was given sufficient time to decide whether I would like to take part in this study or not.

The following topics were discussed in addition to the written information:

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I am aware that this study primarily serves to expand scientific knowledge in the field and that it may not necessarily result in any personal benefit for me.

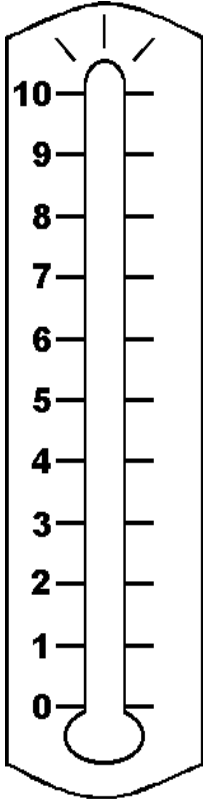
I have been informed that I may withdraw my consent to participate in this clinical study at any time without giving any reasons, without any negative consequences for me. The responsible physician may terminate the clinical study any time if she/he deems it a medical necessity.

Data protection:

I am aware that personal data collected during this clinical study, in particular medical findings, will be recorded, stored and evaluated. The use of my medical data will be in accordance with legal stipulations and requires my voluntary consent prior to my participation in the study. This means that without the following consent, I cannot take part in the clinical study.

- 1. I agree that personal data collected within this clinical study, in particular medical data, will be collected and stored both in paper form and on electronic data storage devices. If necessary, the data collected may be communicated in pseudonymous form (encoded):**
 - a) to the sponsor and a representative of the sponsor responsible for scientific evaluation (study management).**
 - b) in case of adverse events: to the sponsor, the study management, and the ethics committee responsible.**
- 2. In addition, I agree that persons authorized by the sponsor and subject to confidentiality, as well as the regulatory authorities, may access the personal data stored by the investigator, in particular medical data, if this is necessary to verify that the study is being conducted according to protocol. In this respect, I release the investigator from the confidentiality agreement.**
- 3. The consent to the storing and processing of my personal data, in particular my medical data, is irrevocable. I have been informed that I may terminate my participation in the clinical study at any time. In the case that I withdraw my consent to participate in the clinical study, I agree that all data saved until that point may continue to be used if necessary in order to:**
 - a) evaluate the effects of the radiation regimen investigated.**
 - b) ensure that my interests are not affected.**
 - c) provide complete documentation for assessment of radiotherapy for metastatic spinal cord compression.**
- 4. I agree to the condition that my data will be stored for at least 10 years after the end of the study or the termination of my participation therein, as stipulated by guidelines for the conduct of clinical studies. After this period, my personal data will be deleted, except if longer storage periods are required according due to other reasons (law, contracts, constitutions).**
- 5. I have been informed about the following legal requirements: In case that I withdraw my consent to take part in the clinical study, all locations storing my personal data, in particular my medical data, must check whether the data stored for purposes a) to c) are still required. Any data that is no longer required must be deleted without delay.**

Appendix III Distress (quality of life) (JC Holland distress thermometer)

How much distress have you been experiencing <u>in the past week, including today?</u>	Please indicate to what extent you have felt distress on the thermometer and indicate the reasons for this distress below.	
<p style="text-align: center;">Very distressed</p>  <p style="text-align: center;">Not at all distressed</p>	<p>Practical Problems</p> <ul style="list-style-type: none"> <input type="checkbox"/> Living situation <input type="checkbox"/> Insurance <input type="checkbox"/> Work/school <input type="checkbox"/> Transportation <input type="checkbox"/> Child care 	<p>Physical Problems</p> <ul style="list-style-type: none"> <input type="checkbox"/> Pain <input type="checkbox"/> Nausea <input type="checkbox"/> Exhaustion <input type="checkbox"/> Sleep <input type="checkbox"/> Movement/mobility
	<p>Family Problems</p> <ul style="list-style-type: none"> <input type="checkbox"/> Partner <input type="checkbox"/> Children 	<ul style="list-style-type: none"> <input type="checkbox"/> Washing, dressing <input type="checkbox"/> Appearance <input type="checkbox"/> Breathing <input type="checkbox"/> Mouth sores
	<p><u>Emotional Problems</u></p> <ul style="list-style-type: none"> <input type="checkbox"/> Worry <input type="checkbox"/> Fears <input type="checkbox"/> Sadness <input type="checkbox"/> Depression <input type="checkbox"/> Anxiety 	<ul style="list-style-type: none"> <input type="checkbox"/> Food/eating <input type="checkbox"/> Digestion <input type="checkbox"/> Constipation/diarrhoea <input type="checkbox"/> Gastrointestinal changes <input type="checkbox"/> Changes in urination <input type="checkbox"/> Fever
	<p><u>Spiritual/Religious Concerns</u></p> <ul style="list-style-type: none"> <input type="checkbox"/> Relating to God <input type="checkbox"/> Loss of faith 	<ul style="list-style-type: none"> <input type="checkbox"/> Dry/itching skin <input type="checkbox"/> Dry/congested nose <input type="checkbox"/> Tingling in hands and feet <input type="checkbox"/> Feeling swollen <input type="checkbox"/> Sexual problems
<p>Other Problems:</p> <hr/> <hr/>		

Holland, JC. Update: NCCN practice guidelines for the management of psychosocial distress. *Oncology* 1999; 13: 459–507.

Appendix IV**Eastern Cooperative Oncology Group (ECOG) – Performance Status**

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

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Appendix V: Ethics committee vote

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Appendix VI: Insurance