Focused Ultrasound and RadioTHERapy for Non-Invasive Palliative Pain Treatment in Patients with Bone Metastasis: A Study Protocol for the Three Armed Randomized Controlled FURTHER-trial

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Research Article

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Abstract

Background

Cancer Induced Bone Pain (CIBP), caused by bone metastases, is a common complication of cancer and strongly impairs quality of life (QoL). External Beam RadioTherapy (EBRT) is the current standard of care for treatment of CIBP. However, approximately 45% of patients have no adequate pain response after EBRT. Magnetic Resonance image guided High Intensity Focused Ultrasound (MR-HIFU) may improve pain palliation in this patient population.

Methods/design:

The FURTHER trial is an international multicenter, three-armed randomized controlled trial. A total of 216 patients with painful bone metastases will be randomized in a 1:1:1 ratio to receive EBRT only, MR-HIFU only, or combined treatment with EBRT followed by MR-HIFU. During a follow-up period of six months, patients will be contacted at eight time points to retrieve information about their level of pain, QoL and the occurrence of (serious) adverse events. The primary outcome of the trial is pain response at 14 days after completion of treatment. Secondary outcomes include pain response at 14 days after trial enrolment, pain scores (daily until the 21st day, weekly until the 6th week and monthly until the 6th month), toxicity, adverse events, QoL, and survival. Cost-effectiveness and cost-utility analysis will be conducted.

Discussion

The FURTHER trial aims to evaluate the effectiveness and cost-effectiveness of MR-HIFU – alone or in combination with EBRT – compared to EBRT to relieve CIBP. The trial will be performed in six hospitals in four European countries, all of which are partners in the FURTHER consortium.

Trial registration:

The FURTHER trial is registered under the Netherlands Trials Register number NL71303.041.19 and ClinicalTrials.gov registration number NCT04307914. Date of trial registration is 13-01-2020.

Background

Cancer Induced Bone Pain (CIBP) due to bone metastases often results in substantial deterioration of Quality of Life (QoL) in patients with advanced cancer.[1,2] The mainstay of treatment of CIBP are oral analgesics (mostly opioids), in some cases stabilization or fixation surgery and in most cases External Beam RadioTherapy (EBRT).[3–5] Although EBRT is a well-established treatment option, not all patients

experience pain relief after this treatment. A recent systematic review has shown that approximately 45% of patients do not respond to EBRT and if patients do respond, it can take up to six weeks before adequate pain relief is reached.[6–8] Moreover, approximately 50% of initial responders experience recurrent pain, for which re-irradiation is only effective in 58% of patients.[9,10] Fast and effective pain control is paramount to optimize QoL in palliative cancer care. Magnetic Resonance image guided High Intensity Focused Ultrasound (MR-HIFU), as an alternative or addition to EBRT, may improve pain palliation treatment in this patient population, by increasing the percentage of responders, and decreasing the time to response.[11,12]

MR-HIFU is a non-invasive image-guided treatment modality, which can deliver acoustic energy to heat target tissue to ablative temperatures.[11,13] One of many potential applications of MR-HIFU is in palliative pain treatment for CIBP, in which the pain palliation mechanism is hypothesized to be through ablation of periosteal nerves and tumor debulking. Previous studies have shown that pain response may occur within three days after MR-HIFU treatment, and response rates are promising with pain responses ranging from 67–88% of patients.[14–21] Moreover, combining MR-HIFU with EBRT may have a complementary or even synergistic effect on pain response.[22–25] In an earlier study the feasibility of combined treatment was proven.[25]

Still, high quality evidence and context is needed to determine the role of MR-HIFU in the first-line treatment options of patients with CIBP. The FURTHER-consortium sets out to provide this evidence and to evaluate the effectiveness and cost-effectiveness of MR-HIFU (alone or in combination with EBRT) as a palliative treatment option for patients with CIBP caused by bone metastases. To date, no randomized controlled trials have been performed to compare the current standard of care (EBRT) to MR-HIFU or combined treatment. Therefore, we designed a three-armed randomized controlled trial to compare Focused Ultrasound and RadioTHERapy for Noninvasive Palliative Pain Treatment in Patients with Bone Metastases – The FURTHER-trial.

Methods

Study Design

The FURTHER-trial is a multicenter three-armed randomized controlled trial, performed in six hospitals in four European countries, all of which are partners in the FURTHER consortium (appendix). The trial will be coordinated from the UMC Utrecht, with a steering-group consisting of representatives of all institutions and an external advisory board. The design and report of this protocol follow the Standard Protocol Items: Recommendations for Interventional Trials statement.[26]

After inclusion, patients are randomized in a 1:1:1 ratio to one of the three intervention arms and will either receive standard EBRT, MR-HIFU only, or combined EBRT and MR-HIFU (Fig. 1). Treatment will be delivered as soon as possible. A total of 216 patients will be randomized, 72 patients into each arm of the trial. Patients and doctors will not be blinded to treatment and treatment allocation will not be concealed.

Randomization will be done centrally, by a computer generated sequence using variable block randomization method in Castor EDC.[27] Randomization will be stratified by institution and planned EBRT fractionation schedule.

Objectives

The aim of the FURTHER trial is to evaluate the effectiveness and cost-effectiveness of MR-HIFU (alone or in combination with EBRT) compared to EBRT alone for palliation of CIBP. The primary outcome is patient reported pain response fourteen days after completion of treatment (Table 1). Pain response will be based on the numeric rating scale (NRS) and the pain severity index calculated from the Brief Pain Inventory (BPI) questionnaire.[28,29] In addition, analgesic and anti-neuropathic drug use is recorded, and all opioid analgesics are expressed as the oral equivalent daily morphine use (OMED). The primary endpoint of the trial will follow the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone metastases.[30] In accordance with the consensus, pain will be assessed by the worst pain score over the previous three days. Patients will be categorized as responders when either a reduction of pain score of at least 2 points without increase of analgesic intake is achieved, or a reduction of analgesic intake of at least 25% is accomplished without an increase of pain score at the treated site. All other patients will be categorized as non-responders.

Table 1
Primary and Secondary outcomes of the FURTHER-trial, a trial looking at the impact of treatment with MR-HIFU with or without radiotherapy on patients with painful bone metastases.

Primary outcomes	
1.1. Pain response 14 days after completion of treatment	Assessed using the BPI and patient pain-diary. Used to assess effectiveness of treatment
1.2. Pain response at 14 days after inclusion	Assessed using the BPI and patient pain-diary. Used to assess effectiveness of treatment taking hospital logistics and planning into account
Secondary outcomes	
2.1. Patient-reported pain scores	Assessed using the BPI and patient pain-diary during the first twenty-one days, at four and six weeks and three and six months following treatment.
2.2. Physician reported toxicity	Assessed by telephone call at three days, one, four and six weeks, and three- and six-months following completion of treatment according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
2.3. Patient-reported quality of life	Assessed using the EORTC QLQ BM22, C15-PAL and EQ-5D-5L and PGIC at baseline, one, two and four weeks, and three and six months following completion of treatment.
2.4. Local tumour control.	Assessed using CT and/or MRI imaging at patient discretion at three and/or six months after completion of treatment.
2.5. Levels of anxiety and depression	Assessed among patients, patients' partners and caregivers by the Hospital Anxiety and Depression Scale (HADS) and EDIZ-list at baseline, one, two, four and six weeks, and three and six months following completion of treatment.
2.6. Cost-effectiveness of the treatment.	Assessed as cost per responder and cost per quality-adjusted life years (QALY), from a payer perspective, at six months of follow up.

Secondary endpoints (Table 1) will include patient reported pain response at fourteen days after inclusion, as this will reflect the differences in complexities in planning EBRT versus MR-HIFU. Other secondary endpoints include QoL at one, two and four weeks, and three and six months after treatment using validated questionnaires (EORTC QLQ BM22, EORTC C15-PAL, EQ-5D-5L, and PGIC).[31–35] We will also compare the evolution of pain scores between MR-HIFU and EBRT treatment groups (time to pain palliation, time to pain progression, duration of pain palliation). Cost-effectiveness and cost-utility analyses will be performed. Although the primary goal of both interventions will be pain palliation, we will also evaluate local control. Local control will be assessed at three and/or six months for patients for whom MR of computed tomography (CT) imaging is available.

Patient Selection And Follow Up

The study population will consist of male and female adults (age ≥ 18 years) with non-vertebral painful bone metastases that are accessible for MR-HIFU and EBRT who are able to give a written informed consent. Patients will be enrolled at the departments of Radiation Oncology of all participating centers. The radiation oncologist will approach potentially eligible patients who meet the in- and exclusion criteria for study participation (Table 2). (S)he will shortly explain the study (design) and the three treatment strategies (EBRT only, MR-HIFU only, or combined EBRT and MR-HIFU). When patients express interest, they will receive more detailed information about the study. The investigator or an authorized delegate will check with patients whether they have understood the aim and content of the study. Then patients will be requested to sign a written informed consent.

Table 2
Inclusion and exclusion criteria the FURTHER-trial

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Previous surgery on the target location
Patient capable of giving informed consent	Neurological symptoms due to nerve involvement of target lesion
Referral to radiotherapy department due to painful metastatic bone lesion (NRS ≥ 4)	Need for surgery of targeted location due to (impending) pathological fracture
Pain from target lesion is distinguishable from other lesions *	Unavoidable critical structures or dense tissues in target area ***
Target lesion location is accessible for MR-HIFU and EBRT **	Curative intention of treatment plan
Target lesion is visible on pre-treatment MR or CT imaging, with a maximum diameter of 8 cm	Contraindications MRI or sedation
Participant able to fit in the MRI gantry	Participant enrolled in another clinical interventional study related to bone metastases treatment or pain relief treatment
Reasonable performance score (KPS ≥ 50% or Zubrod/ECOG/WHO < 3)	Clinically relevant medical history or physical findings that could interfere with the patient's safety as judged by the treating physician
Life expectancy ≥ 3 months	
** Solitary painful metastatic bone lesion or multiple metastatic lesions with one predominantly painful target lesion (≥ 2 points higher pain score than other lesions).*	
*** e.g.: Extremities, pelvis (os pubis, os ilium, os ischium, sacrum, acetabulum), shoulders, in selected cases ribs and sternum (if no lung tissue in HIFU beam path)*	
**** as judged by the operator. e.g.: nerve bundles, skin, extensive scarring, non-targeted bones, air (e.g. hollow viscera), (external) fixation device* *Abbreviations: ECOG, KPS etc HIFU EBRT*	

Given the urgent need for rapid pain relief, patients will be allowed to make a decision for participation in the study and sign an informed consent immediately after receiving the information. The researcher will randomize the patient using the online Castor EDC database.[27] The treatment arm allocation will immediately be shown. Patients will be treated according to the treatment arm they are assigned to.

To retrieve information about their level of pain, QoL and (serious) adverse events, patient outcome measures will be assessed at several time points during a follow-up period of six months (Table 3). Starting on the treatment day, a patient diary will be used for self-reporting of pain levels and pain medication use during the first 21 days following start of treatment, and at one, three and six months. The diary will be supplied and explained to patients prior to the treatment. Furthermore, patients will also be interviewed or contacted by telephone at baseline, and at one, two, four and six weeks, and three, and six months to assess pain response, patient reported QoL and (serious) adverse events. A data management plan is in place to ensure data quality and a dedicated data-management team located at the UMC Utrecht will ensure data security, coding and storage. Quality and completeness of data will be monitored by an independent team of trained data-monitors.

Table 3
Follow up timeline in the FURTHER trial

	Ti	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**
	Incl	Tx	3d	7d	14di	14d	4w	6w	3m	6m
Informed consent	**x**									
Baseline data	**x**									
Patient diary *		**x**	**x**	**x**	**x**	**x**				
Brief Pain Inventory	**x**						**x**	**x**	**x**	**x**
Assesment Adverse Events (by telephone)			**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Quality of life questionaires **		**x**		**x**		**x**	**x**	**x**	**x**	**x**
Anxiety and depression in patient / partner / caregiver (HADS + EDIZ)		**x**		**x**		**x**	**x**	**x**	**x**	**x**
Patient Global impression of Change score				**x**	**x**	**x**	**x**	**x**	**x**	**x**
CT and/or MRI ***		**x**							**x**	**x**
* First 21 days after treatment. Contains daily BPI's and weekly PROM's										
** EORTC QLQ BM22, EORTC QLQ C15-PAL, EQ-5D-5L										
*** At patient discretion										

Patients are free to leave the study at any time. The investigator can decide to withdraw a patient from the study for urgent medical reasons. Patients will be considered as non-responders when they will be referred to alternative palliative treatments of the treated metastasis (such as (re)irradiation, radiopharmaceuticals, surgery, cryotherapy, radio-frequency ablation or nerve blocks, or MR-HIFU in the EBRT arm).

Study Procedures

Radiotherapy treatment

Control patients will undergo standard radiotherapy for painful bone metastases. The radiation schedule is at the discretion of the treating radiation oncologist. The radiation oncologist may decide to administer a single fraction EBRT of 8 Gy, a multi-fraction regime of 20 Gy in 5 fractions, 24 Gy in 6 fractions or 30 Gy in 10 fractions. A planning CT with or without contrast agent in treatment position will be taken for target delineation. Treatment plans may be delivered using Intensity-Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Radiotherapy (VMAT) or Stereotactic Body Radiation Therapy (SBRT) technique. Plans will be accepted if at least 90% of the planning target volume (PTV) will receive 95% of the prescribed dose (V90 > 95%). Typically, a 10-millimeter isotropic PTV margin will be used. A maximal 3D dose of 110% will be allowed. The maximum allowed dose in organs at risk will be determined according to local institution's protocol. Position verification is at the discretion of the treating radiation oncologist in consultation with the clinical physicist. It is encouraged to use online position verification by use of cone beam CT at every fraction.

MR-HIFU treatment

MR-HIFU treatment will be delivered on a clinical MR-HIFU system (Sonalleve™ System V2, Profound Medical Corp, Mississauga, Canada or Exablate™ 2100, Insightec, Tirat Carmel, Israel), integrated into a 1.5 or 3T MR scanner (Achieva™, Ingenia™, Philips Healthcare, Best, The Netherlands, or Signa™, GE Healthcare, Milwaukee, WI, USA). MR-HIFU treatment will aim at ablating the periosteum followed by ablation of the bone metastasis if feasible and safe. HIFU treatment will be performed in accordance with the international consensus paper.[12]

During treatment preparation, the skin overlying the site of interest will be shaved and premedication (consisting of analgesics) will be administered. The procedure will be done using either procedural sedation and analgesia or general anesthesia. Patients will be positioned to obtain an HIFU beam path as perpendicular to the cortical bone surface as possible. After treatment planning and patient positioning, a low-energy sonication test will be performed to confirm reachability and correct for potential HIFU beam path distortion. Maintaining a temperature of at least 55°C for 1 second as measured by MR-thermometry in front of the cortical bone is considered to deliver a thermal dose high enough to achieve adequate ablation of the periosteum.[36,37] During treatment, real-time temperature mapping will be used to monitor whether this goal was achieved and to determine completion of treatment. Preferably full lesion surface

coverage will be achieved by systematically sonicating treatment cells in a contiguous way, respecting system recommended cooling times between sonications. After the HIFU procedure, a contrast-enhanced T1w-scan using a gadolinium-based standard MR contrast agent will be acquired to evaluate treatment effect. The patients are then transferred to the recovery room or patient ward for medical supervision. When the patient has recovered from procedural sedation and no complications have occurred, the patient can be discharged. Alternatively, patients may, at the discretion of treating physician, stay overnight at the hospital. If MR-HIFU treatment does not alleviate pain within four weeks after treatment, patients will be offered standard care (EBRT).

Combined treatment

Patients allocated to the combined intervention arm will undergo both interventions as described above. In the (or “a” or “our”) previous research, it was shown that the combined treatment of EBRT and MR-HIFU is feasible and safe.[25] Clinical outcomes were promising and need to be further assessed in this comparative trial.

In the combination treatment arm, both treatments will be planned as soon as possible following inclusion (preferably within one week), to ensure rapid pain palliation. The pre-treatment appointments will be planned in a way that is least burdensome for the patient. Therefore, flexible planning of pre-operative screening and MR-HIFU treatment to minimize extra hospital visits is encouraged. A flowchart of the workflow for both single fraction and multifraction EBRT is given in appendix. To ensure an efficient workflow for the combined arm, a weekly available MR-HIFU slot is advised.

Analgesic medication

Patients may receive pain medication and/or dexamethasone as required by their symptoms, both before and after the EBRT and/or MR-HIFU treatment. The amount of pain medication used is part of the primary and secondary endpoints of the study and will be recorded at baseline before treatment and during follow-up. During the MR-HIFU treatment, the patient will receive hypnotic and analgesic agents under the direct supervision of an anesthesiologist or sedationist for pain control and to ensure a stable patient position during treatment. Drug selection will be based on practitioner preference.

Sample Size Calculation

The study is powered to detect a difference in proportions of patients with pain response of the treated bone metastasis at fourteen days after completion of treatment. For this purpose, the two MR-HIFU arms will be combined. We need 72 patients in each arm to achieve a power of 90%, using a one-sided alpha of 5% and assuming a 10% post-randomization drop out. We base this calculation on previous research showing that the proportion of patients with successful pain palliation at fourteen days following end of treatment is 0.69 for MR-HIFU and 0.40 for EBRT.[9,14] We conservatively assume that 10% of patients allocated to one of the MR-HIFU arms will not be able to undergo MR-HIFU and will therefore receive EBRT.

Statistical Analysis

All statistical analyses will be performed using IBM SPSS statistics, version 24 (IBM Corp. Armonk, N.Y., USA) and R version 4.0.4 (R foundation for statistical computing; https://R-project.org/). Data characterized by normal distribution will be expressed as means with standard deviations. Parameters not normally distributed will be expressed as medians with the interquartile ranges. Data will be analyzed according to the intention to treat principle. In case of post-treatment dropout (i.e. patients not surviving longer than a week, or patients unable to provide pain scores and analgesic use), a worst-case analysis will be performed, where dropped-out patients will be classified as non-responders.

The primary outcome (i.e. (proportion of) patients with pain response at fourteen days following completion of treatment) will be presented in percentages. Differences in pain response between arms will be compared by χ^2-test. We will also conduct a time-to-event analysis for pain response. Differences in overall survival will be analyzed by Kaplan-Meier analysis. Toxicity will be presented as the overall incidence of CTCAE grade 3–4 toxicity and differences will be tested with the χ^2-test. QoL will be compared between the three groups at three and six months after treatment completion. A change of 10% of the scale breadth will be considered a clinically relevant change in QoL. We will evaluate the pattern of QoL as a continuous outcome over time using mixed models. Differences with a P-value of < 0.05 will be considered statistically significant.

For the cost-effectiveness analysis, primary outcome will be presented as cost per responder. Quality-adjusted life years (QALYs) will be derived from the EQ-5D-5L questionnaires to be applied in the cost-utility analysis. The costs of MR-HIFU and EBRT will be calculated using an actual cost accounting approach.

Adopting a payer perspective, we will calculate the incremental cost-effectiveness and cost-utility ratios at six months of follow-up. Deterministic and probabilistic (i.e., bootstrapping) sensitivity analysis will be conducted to test the robustness of the results. Because of the short timeframe, discounting will not be considered.

Discussion

In this report, we present the rationale and design of the FURTHER-trial. The aim of this international three-armed randomized controlled trial is to evaluate the effectiveness and cost-effectiveness of MR-HIFU – alone or in combination with EBRT – compared to EBRT as a palliative treatment option to relieve CIBP. Although standard of care EBRT is a well-established treatment option, only approximately 55% of patients experience adequate pain relief after treatment.[6] MR-HIFU may improve pain palliation treatment for patients with painful bone metastasis, by providing fast and durable pain response in a higher percentage of patients[14]. Effectiveness and safety of MR-HIFU (alone or in combination with EBRT) as first-line treatment have never been compared to EBRT alone in an RCT.

MR-HIFU treatment provides a non-invasive, radiation-free treatment option for patients with CIBP caused by bone metastases. The treatment can be done in a single session and can be repeated multiple times if necessary. Preliminary clinical studies on the use of MR-HIFU for palliation of painful bone metastases demonstrated excellent response rates and safety.[13–21] Hurwitz et al (2014) reported results of a multicenter randomized placebo-controlled trial to evaluate safety and efficacy of MR-HIFU for treating bone metastases that were painful despite previous radiotherapy, were unsuitable for radiotherapy or who declined radiotherapy.[14,38] Response to MR-HIFU was rapid, with about two-thirds of patients reporting pain response within a few days after treatment. Lee et al (2017) performed a single-center matched-pair study which showed that MR-HIFU provides a similar overall treatment response rate but faster pain relief compared to EBRT and thus has the potential to serve as the first-line treatment for painful bone metastasis in selected patients.[18] Harding et al (2018) evaluated QoL after MR-HIFU for painful bone metastasis and showed that there was a substantial positive effect on physical functioning and symptoms .[39]

MR-HIFU is considered a non-invasive low risk intervention. There are however aspects of the treatment that make it a more complex treatment strategy for pain palliation. Currently not all bone metastases are targetable with MR-HIFU (e.g., vertebrae). Close collaboration and good communication between the departments of radiation oncology and radiology is necessary for rapid referral and eligibility screening. In addition, patients will be under sedation during the MR-HIFU treatment. The use of sedation or general anesthesia for the MR-HIFU treatment has two major advantages. First, patients will lie completely still during the entire treatment, which decreases the risk of side effects and impaired treatment efficacy due to patient motion. Second, patients experience less discomfort and pain during MR-HIFU treatment. The risk of sedation is very low. However, to enable sedation, MR-HIFU treatment requires one-day hospitalization, and some patients will have an extra hospital visit for the pre-procedural anesthesiologic screening. The planning of complex procedures in the palliative setting, where patients need to be treated as soon as possible is challenging.

Since planning of MR-HIFU is more complex and logistically more challenging than EBRT, we have incorporated patient reported pain response at 14 days after inclusion as secondary endpoint. This way the FURTHER-trial will provide insight into the real advantages and challenges of MR-HIFU from the patient’s perspective as well.

List Of Abbreviations

BPI	Brief Pain Inventory
CIBP	Cancer Induced Bone Pain
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EBRT	External Beam RadioTherapy
ECOG	Eastern Cooperative Oncology Group
EDIZ	Ervaren Druk door Informele Zorg
EORTC C15-PAL	European Organisation for Research and Treatment of Cancer C15 Palliative questionnaire
EORTC QLQ BM22	European Organisation for Research and Treatment of Cancer Bone Metastases questionnaire
EQ-5D-5L	EuroQol 5-level evaluation questionnaire
FURTHER	Acronym: Focused Ultrasound and radioTHERapy for pain palliation in patients with painful bone metastasis
HADS	Hospital Anxiety and Depression Scale questionnaire
HIFU	High Intensity Focused Ultrasound
IMRT	Intensity-Modulated Radiation Therapy
KPS	Karnofsky Performance Score
MR	Magnetic Resonance
MR-HIFU	Magnetic Resonance guided High Intensity Focused Ultrasound
NRS	Numeric Rating Score
OMED	Oral equivalent daily morphine use
PTV	Planning Target Volume
QoL	Quality of Life
RT	Radiotherapy
SBRT	Stereotactic Body Radiation Therapy
QALY	Quality-adjusted life years
SPSS	Statistical Package for the Social Sciences
VMAT	Volumetric Modulated Arc radioTherapy
WHO	World Health Organisation

Declarations

Ethics approval and consent to participate

The FURTHER trial is registered under the Netherlands Trials Register number NL71303.041.19 and ClinicalTrials.gov registration number NCT04307914. Date of trial registration is 13-01-2020. This protocol is version 2 developed on 13 January 2020. The FURTHER trial has Ethical Approval in all participating centres and has started inclusion in multiple participating centres from 10-03-2020. Any protocol amendments will be tracked, dated and logged in the trial registry. Recruitment is expected to be completed by 10-03-2023.

Consent for publication

Not applicable

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Conflict of interest Statement

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Data Availability Statement

All research data for this work are stored in an online repository and will be made available upon reasonable request to the corresponding author.

Authors' contributions

CB, LB, MFB, IM, AM, MB, HG, GB, RBS, HM, AN, AB, DM, MNB, CM, HV conceived the study and contributed to the design of the study. MMB, CF, DS drafted and critically revised the manuscript. All authors provided important intellectual input, revised and approved the final manuscript.

Authors' information

See titlepage.

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Figures

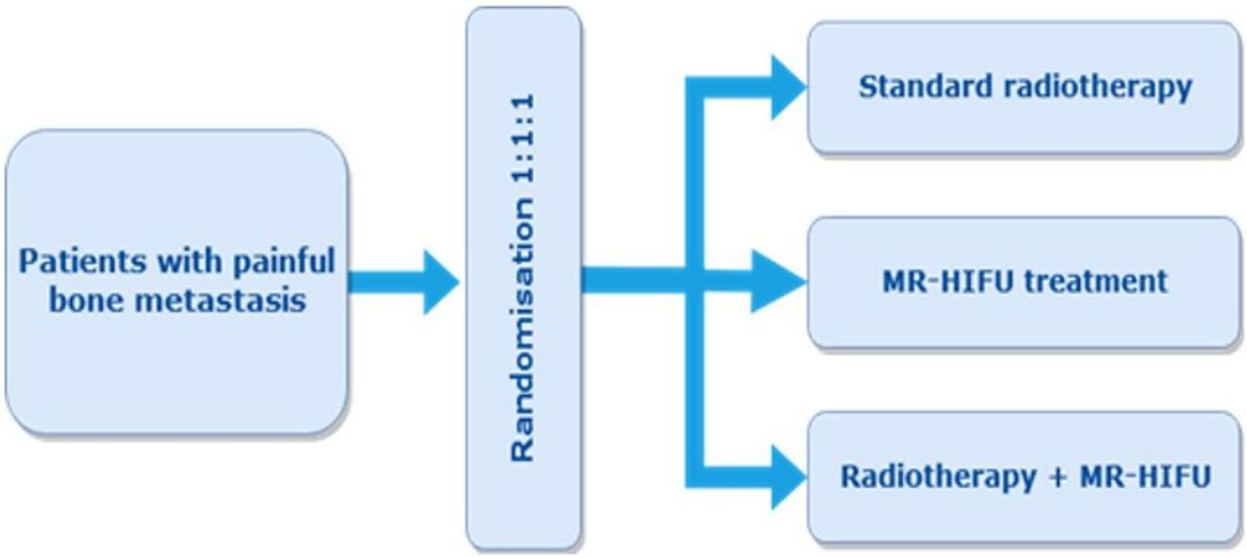

Figure 1

Flowchart of the FURTHER-trial randomisation design

Supplementary Files

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