Wiley
International Journal of Clinical Practice
Volume 2025, Article ID 4962457, 11 pages
https://doi.org/10.1155/ijcp/4962457

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Research Article

Eligibility for Magnetic Resonance-Guided High Intensity Focused Ultrasound in Patients Referred for Radiotherapy on Painful Nonspinal Bone Metastases

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Received 17 July 2024; Accepted 11 April 2025

Academic Editor: Nikhat Kaura

Purpose: This prospective observational study aims to investigate which proportion of patients with bone metastases referred for External Beam Radiation Therapy (EBRT) would be able to undergo Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) as alternative to EBRT, and to examine reasons for ineligibility.
Materials and Methods: Adult patients with nonspinal bone metastases referred to four radiotherapy departments were included. Local, multidisciplinary teams assessed which patients would be eligible for MR-HIFU. The main reason(s) for ineligibility were categorized as patient-related or lesion-related. A random subsample of 30 ineligible patients were analyzed in detail to identify all reasons of ineligibility.
Results: Overall, 57 of 741 (8%) nonspinal bone lesions were eligible for MR-HIFU as alternative to EBRT. In total, 153 lesions (21%) in 130 patients were ineligible because of patient-related factors, including curative treatment intent for oligo-metastatic disease (10%), and poor performance status (8%). Of the remaining 588 bone metastases in 526 patients, 531 lesions (470 patients) were ineligible because of lesion-related factors, including 'lesion too extensive/advanced' (29%), '(impending) pathological fracture' (15%), 'no moderate/severe pain from target lesion' (11%). Proportion of ineligibility varied between centers from 70% to 96%, which was mainly attributable to differences in patient-related factors. Within the random subsample of 30 ineligible patients, 27 patients had multiple reasons for ineligibility.
Conclusion: A small proportion of patients, referred for EBRT of bone metastases, would be eligible to undergo MR-HIFU as alternative palliation option. Taken together, patients presenting with small, localized lesions in nonspinal regions, primarily seeking pain relief without additional treatment goals are the most promising candidates for this therapy. These factors could be used to triage patients eligible for MR-HIFU, thereby reducing unnecessary screening efforts, enhancing patient selection, and ultimately improve patient management strategies by optimizing the use of MR-HIFU as a treatment option.

1. Introduction

Bone metastases are a common complication of cancer, with an incidence ranging from 30% to 75% depending on the primary tumor type [1–4]. They are particularly prevalent in prostate and breast cancer, where more than 70% of patients with advanced disease develop bone involvement [1–4]. Approximately 80% of patients with bone metastases experience moderate to severe pain, which can be debilitating and substantially impacts patients' quality of life [5–7]. Fast and effective pain control is crucial to optimize palliative care. External beam radiotherapy (EBRT) is currently widely used as local-regional treatment for pain palliation in patients with painful bone metastases [8]. Downsides of EBRT are that median time to induce adequate pain relief is 4 weeks, only 60% of patients experience pain relief, and more than half of responders develop recurrent pain [9, 10]. Options for reirradiation may be limited due to decreased effectiveness and the cumulative radiation doses delivered to sensitive structures [11–13]. Systemic treatment options, such as opioids, nonsteroidal anti-inflammatory drugs, radioisotopes, and bisphosphonates are associated with (even severe) side effects [8]. Therefore, there is room for improvement in local treatment aimed at pain reduction and improved patients' quality of life [14].

Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) is a promising alternative for pain management in patients with nonspinal bone metastases [12, 13, 15, 16]. In contrast to other interventional management methods such as radiofrequency ablation, cryoablation, image-guided nerve block, and embolization, MR-HIFU is a noninvasive treatment. It uses focused acoustic energy to heat tissue in a specific target area guided by MR images [11–13, 15, 16]. In bone metastases, this can be used for the ablation of the periosteal nerves and debulking of the tumor, while sparing surrounding healthy tissue [11, 14]. Clinical studies have reported rapid and long-lasting pain relief after MR-HIFU, with pain response rates ranging from 64% to 88% [11, 16–24]. However, the superior effectiveness of MR-HIFU over EBRT in terms of early pain response, as well as the effectiveness of their combination, is currently topic of study [25]. The ongoing FURTHER project, comparing the (cost-)effectiveness of MR-HIFU alone, MR-HIFU combined with EBRT, and standard of care (i.e., EBRT) in a three-armed randomized controlled trial (RCT), will give insights into these aspects [25, 26].

Despite the growing adoption of MR-HIFU, its applicability is limited by several clinical factors, such as the need for deep conscious sedation or general anesthesia, and the relatively long treatment times. Also technical factors, such as restrictions on lesion location and maximum size to be accessible by MR-HIFU, may limit its applicability. These factors have implications for implementation of MR-HIFU and raise the question of which role MR-HIFU could fulfill in the first-line management of painful nonspinal bone metastases. Robust data on the real-world applicability and patient eligibility for MR-HIFU is lacking. Currently, the proportion of eligible patients for MR-HIFU treatment is unknown. By quantifying this proportion of eligible patients, this study aims to provide insights into its potential impact for the growing population of patients with painful bone metastases. In addition, establishing causes of ineligibility will help navigate further research aiming at increasing availability and accessibility of MR-HIFU. Therefore, the aim of this study is to identify the proportion of patients with nonspinal bone metastases that are eligible for MR-HIFU as a stand-alone alternative to EBRT, and to assess reasons of ineligibility.

2. Materials and Methods

2.1. Study Design. The current study was conducted within the context of the European Commission funded FURTHER trial: an international multicenter RCT investigating the effect of MR-HIFU as alternative or addition to EBRT in patients with painful nonspinal bone metastases [25]. Local ethics committees in all participating centers approved the FURTHER trial. For the current analyses, we included data from four centers in the Netherlands, Italy, and Finland, including three university hospitals, and one large teaching hospital. This study was conducted in accordance with the STROBE guidelines [27].

2.2. Patient Selection and Screening. All adult patients with nonspinal bone metastases from solid tumors, regardless of tumor histology, referred to the radiotherapy departments of the participating centers for EBRT of one or multiple bone metastases (not necessarily treated with EBRT), were screened for eligibility for MR-HIFU treatment. The screening process varied across the institutions. At each center, the local team on duty, consisting of radiation oncologists, radiologists and/or clinical researchers screened the referred patients. In centers A and C, all patients referred for radiotherapy treatment of nonspinal bone metastases were considered, while in centers B and D, a preselection took place, where a medical planner selectively referred potential patients to the rest of the screening team based on available clinical data. In all cases, we assessed whether a patient could be treated with MR-HIFU based on the specific system and clinical protocols in place at the participating center. In centers A and D, patient eligibility was assessed based on a Sonalleve system with a 60 cm bore size, while center B utilized a 70 cm bore, and center C employed the ExAblate 2100 (Conformal Bone) system by Insightec.

2.3. Data Acquisition. In each center, patients were prospectively recorded in a screening list. All patients were pragmatically screened based on the (in)eligibility criteria (Table 1). A comprehensive overview of (in)eligibility criteria is given in Supporting Table 1. For patients who were ineligible, the first appearing reason(s) of ineligibility was/were noted. Thereafter, the reason(s) were categorized as patient-related or lesion-related factors. Patient-related factors refer to specific attributes that, regardless of the nature of the metastasis, make MR-HIFU treatment unfeasible for that individual, i.e., curative treatment intent for oligo-metastatic disease, poor physical or mental condition,

or contra-indication for MRI. It was also determined whether it was technically feasible to perform MR-HIFU treatment on the target metastasis, based on lesion-related characteristics, i.e., location, size, extent of metastasis, or cortical involvement.

For many patients, multiple reasons for ineligibility were present. Therefore, a random subsample of 30 ineligible patients from centers A, C, and D was drawn. For this, each ineligible patient was assigned a consecutive number, and an online random number generator was used to select the patients. The local teams identified all different causes of ineligibility in a detailed analysis.

2.4. Data Analysis. Descriptive statistics were used to describe the proportion of eligible lesions for MR-HIFU, which was defined as the number of lesions pragmatically found to be eligible for MR-HIFU divided by the total number of screened lesions. Confidence intervals for these binomial proportions were calculated using the Clopper–Pearson method [28, 29]. Furthermore, the counts for each of the ineligibility criteria, along with their corresponding percentages, were calculated for both patient-related and lesion-related characteristics. Results stratified by center were presented. All analyses were performed using R Studio software (version 2022.12.0).

3. Results

Overall, 656 patients were included in whom 741 nonspinal bone metastases were screened (367/439 in center A, 18/20 in center B, 114/125 in center C, and 157/157 in center D) (Figure 1). The main locations of target bone metastases were pelvic bones ($n = 278$, 49%), femur ($n = 74$, 13%), ribs ($n = 56$, 10%), sacrum ($n = 46$, 8%), humerus ($n = 40$, 7%), and scapula ($n = 36$, 6%). Lesion locations were not reported in one center, leading to 157 cases with unknown locations. A total of 153 lesions (21%) in 130 patients were ineligible due to patient-related factors with curative treatment intent ($n = 76$, 10%) and poor performance status ($n = 56$, 8%) being mentioned most often (Table 2). Of the remaining 588 bone metastases, 531 (in 470 patients) were ineligible for MR-HIFU due to lesion-related factors. Most important reasons were 'target lesion too extensive/advanced' ($n = 212$, 29%), '(impending) pathological fracture' ($n = 114$, 15%), and 'no moderate/severe pain from target lesion' ($n = 80$, 11%) (Table 2). In the end, MR-HIFU could serve as an alternative treatment to EBRT in 57 of 741 lesions (8%). An example of one eligible and two ineligible cases is shown in Figure 2.

The overall proportion of patients eligible for stand-alone MR-HIFU treatment was 8% [6%–10%]. The proportion varied substantially between centers: from 4% to 30% (Table 2). The proportion of ineligibility reasons per participating site is also presented in Table 2.

In the random subsample of 30 ineligible patients who were analyzed in detail, fifteen had a lesion in the pelvic bones, five had a femur lesion, four had a scapula lesion, four a sacrum lesion, one a sternum lesion, and one a lesion in the ribs. All except three patients had more than one reason for ineligibility. For all patients, MR-HIFU treatment was unfeasible due to one or more lesion-related characteristics (e.g., 'target lesion too extensive/advanced' ($n = 15$), 'soft tissue involvement' ($n = 11$), and/or 'not accessible by MR-HIFU' ($n = 10$)) (Table 3). In 14 of these patients (47%), patient-related characteristics (e.g., 'curative treatment intent' ($n = 6$), or 'poor performance status' ($n = 5$)) were identified as reasons for ineligibility for MR-HIFU treatment.

4. Discussion

MR-HIFU is a complex procedure with, at present, restrictive requirements for both patients, including the ability to undergo sedation and long treatment, and lesions, such as lesion location and size [17]. This study shows that less than 10% of patients with nonspinal bone metastases, who are referred for treatment of bone metastases by EBRT, is eligible for MR-HIFU as a stand-alone alternative therapy.

Our results are in line with a retrospective review of the enrollment process of a clinical trial on MR-HIFU ablation for recurrent malignant and locally aggressive benign solid tumors [30]. Lau et al. assessed MR-HIFU eligibility based on clinical (patient-related) and technical (lesion-related) criteria and reported that 31 (85%) of 36 screened patients were excluded [30]. Most patients (18/31) in their study were excluded based on clinical (patient-related) factors that were unrelated to the lesion to be treated. The other ineligible patients (13/31) were technically ineligible for MR-HIFU treatment. On the contrary, Bing et al. examined the targetability of MR-HIFU on painful bone metastases within the Interventional Radiology department of a single center, and found that 36% of the metastases were suitable [31]. However, they only considered this from a planning point of view and did not take patient characteristics into account. In contrast, we included all referred patients for EBRT, which stems from the fact that we conducted this study as part of the FURTHER trial.

Notably, over 70% of lesions are not eligible for MR-HIFU due to lesion-related characteristics. The criteria 'too extensive/advanced,' '(impending) pathological fracture,' and 'no moderate/severe pain from target lesion' are the most important, together accounting for more than half of all excluded lesions. Interestingly, these three criteria represent different underlying concepts: (1) the technical limitations of the MR-HIFU treatment, (2) the different treatment goals of MR-HIFU and EBRT, and (3) the primary objective of the MR-HIFU treatment (targeted pain relief), respectively. The other ineligibility criteria, which are all present to a lesser extent, can almost all be attributed to one of these concepts as well.

Future advancements in MR-HIFU technology could significantly enhance its clinical applicability by addressing the current barriers of the first ineligibility-concept (i.e., the technical limitation of the MR-HIFU treatment). Improvements in techniques and technology such as larger MR bores, modular devices, and per-procedural pain management, may allow for eligibility of more patients in the

Table 1: Eligibility criteria for MR-HIFU treatment in patients having painful nonspinal bone metastases.

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Lymphoproliferative disorders
Nonspinal or nonskull lesion*	MR(-HIFU) or sedation contra-indication**
Moderate or severe pain from target lesion (NRS ≥ 4)	(Impending) pathological fracture
Sufficient condition (KPS > 50%, WHO < 3)	Unavoidable critical structures or dense tissues in target area
Exclusively palliative intent of treatment	Neurological symptoms due to nerve involvement of target lesion
Patient-localized pain with a distinct pathological substrate on recent CT/MRI	Need for surgery of targeted location or recent surgery performed
Target lesion location is sufficiently accessible for MR-HIFU to expect clinical response, as judged by the (interventional) radiologist	

Note: Adapted from [25].

Abbreviations: KPS = Karnofsky performance scale, MR-HIFU = magnetic resonance-guided high intensity focused ultrasound, NRS = numeric pain rating scale, WHO = World Health Organization performance score.

*Including sacrum lesions as these are potentially eligible based on the ability to target them effectively and safely with MR-HIFU without the risk of damaging surrounding nerves.

**Including claustrophobia, the presence of heart pacemakers, or other implanted metal devices.

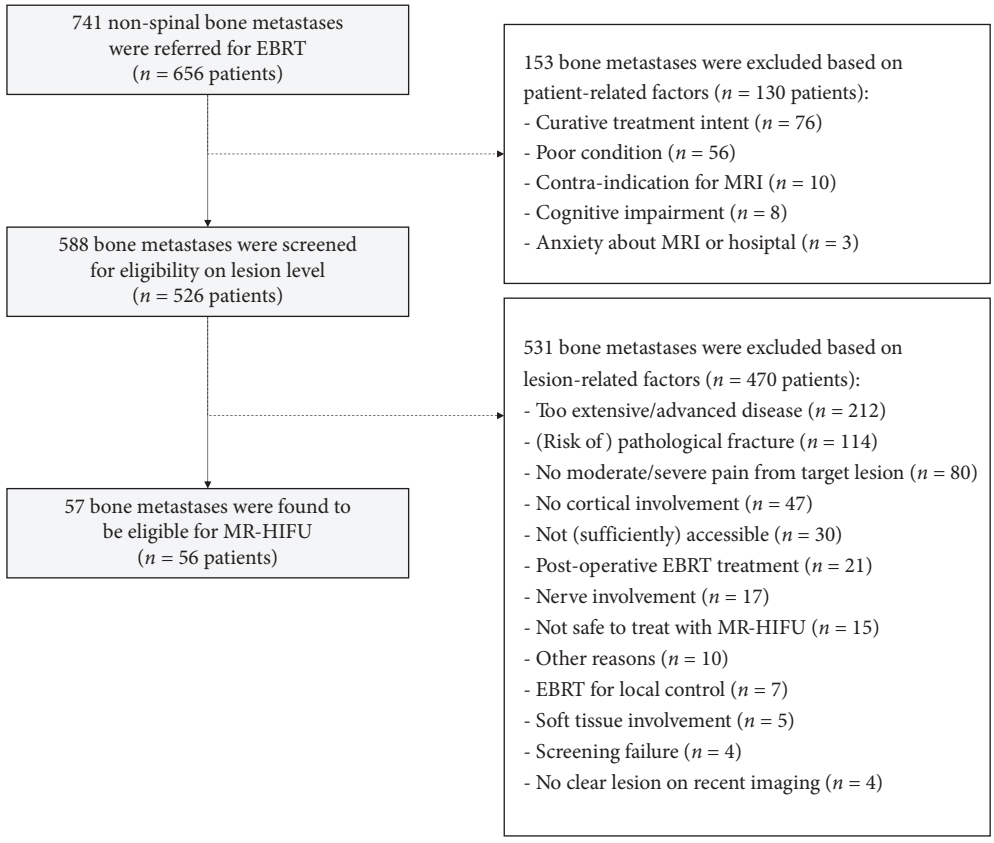

Figure 1: Flowchart of (in)eligibility for MR-HIFU for painful nonspinal bone metastases. Note that the sum of the subcategories may not be equal to the indicated number since more than one reason was applicable for some cases. Abbreviations: EBRT = external beam radiotherapy, MR-HIFU = MR-guided high intensity focused ultrasound, MRI = magnetic resonance imaging.

context of bone metastases [32]. These technical improvements might reduce the proportion of ineligible patients in 'too extensive/advanced' (by improved techniques), 'not accessible by MR-HIFU' (by larger bores or modular devices), and 'poor condition' (by less invasive per-procedural pain management) categories. Additionally, higher-intensity ultrasound (US) beams, innovations such as higher resolution US-HIFU, and improved imaging resolution might enable better targeting of complex or deep-seated lesions. These advancements hold promise for increasing patient eligibility ('not accessible by MR-HIFU' patients) and broadening the clinical impact of MR-HIFU.

The second important concept for ineligibility of MR-HIFU as alternative to EBRT is the fact that EBRT serves other purposes than pain palliation only (exclusion reasons: 'curative treatment intent,' '(impending) pathological fracture,' 'post-operative EBRT,' and 'local control'). For example, curative treatment is pursued when there is oligometastatic disease. Patients with oligo-metastatic disease have good survival when appropriately treated with high doses of radiation (stereotactic body radiotherapy), which aims to achieve long-term disease control [33, 34]. In addition, weak evidence is available regarding HIFU's ability to increase bone density (remineralization) of lesions with (impending) fractures in contrast to EBRT. In such cases, MR-HIFU is not (yet) an alternative to EBRT, and therefore, all these cases remain ineligible for MR-HIFU treatment at present. Future studies (such as the registry arm of the FURTHER RCT [35]) should be conducted to investigate the potential of MR-HIFU to serve alternative treatment goals in addition to pain palliation, as well as explore the long-term effects of MR-HIFU to enhance understanding of its impact on disease control and remineralization, potentially allowing for more patients to be eligible.

The third concept, targeted pain relief, addresses two aspects. First, the presence of pain is a prerequisite for MR-HIFU, as the treatment is (currently) designed to alleviate pain. In our study, more than one-third of the exclusions in centers B (35%) and C (34%) were based on a low pain score (NRS < 4), while this reason accounts for only 5% of the exclusions in the other two centers. Numerous studies examining pain prevalence across various patient populations in European countries have yielded conflicting results [36–38]. This inconsistency, on the one hand, highlights the challenge of measuring the highly subjective nature of pain, and on the other hand, affirms the presence of distinct international differences. Variations in pain management approaches, the prescription and use of pain medications, and the frequency of referrals for radiotherapy in cases of painful bone metastases among different countries could potentially contribute to these observed differences [37, 39]. This suggests that in some countries, it may be necessary to consider patient populations outside the radiotherapy referrals (as the indication for pain management appears to be

Table 2: Numbers of (in)eligibility for MR-HIFU for painful nonspinal bone metastases.

	Center A		Center B		Center C		Center D		Total lesions	
	Dec 2021–Dec 2023		Jan 2022–May 2023		Feb 2021–Sept 2022, Nov 2022–Jun 2023		Sept 2020–Oct 2021, Dec 2022–May 2023			
Lesions screened	**439**	**100%**	**20**	**100%**	**125**	**100%**	**157**	**100%**	**741**	**100%**
Lesions excluded based on patient-related factors*	**113**	**26%**	**1**	**5%**	**16**	**13%**	**23**	**15%**	**153**	**21%**
Curative treatment intent	61	14%	0	0%	8	6%	7	4%	76	10%
Poor condition	47	11%	0	0%	6	5%	3	2%	56	8%
Contra-indication for MRI	1	0%	1	5%	2	2%	6	4%	10	1%
Cognitive impairment	2	0%	0	0%	0	0%	6	4%	8	1%
Afraid of MRI/hospital	2	0%	0	0%	0	0%	1	1%	3	0%
Lesions excluded based on lesion-related factors*	**307**	**70%**	**13**	**65%**	**98**	**78%**	**113**	**72%**	**531**	**72%**
Too extensive/advanced	99	23%	3	15%	34	27%	76	48%	212	29%
(Impending) pathological fracture	80	18%	1	5%	11	9%	22	14%	114	15%
No moderate/severe pain	23	5%	7	35%	42	34%	8	5%	80	11%
No cortical involvement	30	7%	3	15%	0	0%	14	9%	47	6%
Not accessible by MR-HIFU	24	5%	0	0%	4	3%	2	1%	30	4%
Postoperative EBRT	18	4%	0	0%	3	2%	0	0%	21	3%
Nerve involvement	16	4%	0	0%	0	0%	1	1%	17	2%
Not safe to treat with MR-HIFU	13	3%	1	5%	0	0%	1	1%	15	2%
Other reasons	7	2%	0	0%	1	1%	2	1%	10	1%
Local control	6	1%	0	0%	0	0%	1	1%	7	1%
Soft tissue involvement	4	1%	1	5%	0	0%	0	0%	5	1%
Screening failure	4	1%	0	0%	0	0%	0	0%	4	1%
No clear lesion on imaging	1	0%	0	0%	3	2%	0	0%	4	1%
Lesions eligible for MR-HIFU***	**19**	**4% [3–7]**	**6**	**30% [12–54]**	**11**	**9% [4–15]**	**21**	**13% [8–20]**	**57****	**8% [6–10]**

Note: The bold values indicate the totals of the different categories.

Abbreviations: EBRT = external beam radiotherapy, MR-HIFU = MR-guided high intensity focused ultrasound.

*There were some cases that had multiple reasons. Therefore, the sum of the subcategories may not be equal to the overall number indicated. Percentages may not add up to 100% or subtotal due to rounding.

**One patient was eligible for two different lesions.

***Total lesions eligible for MR-HIFU is presented as counts, % [confidence interval].

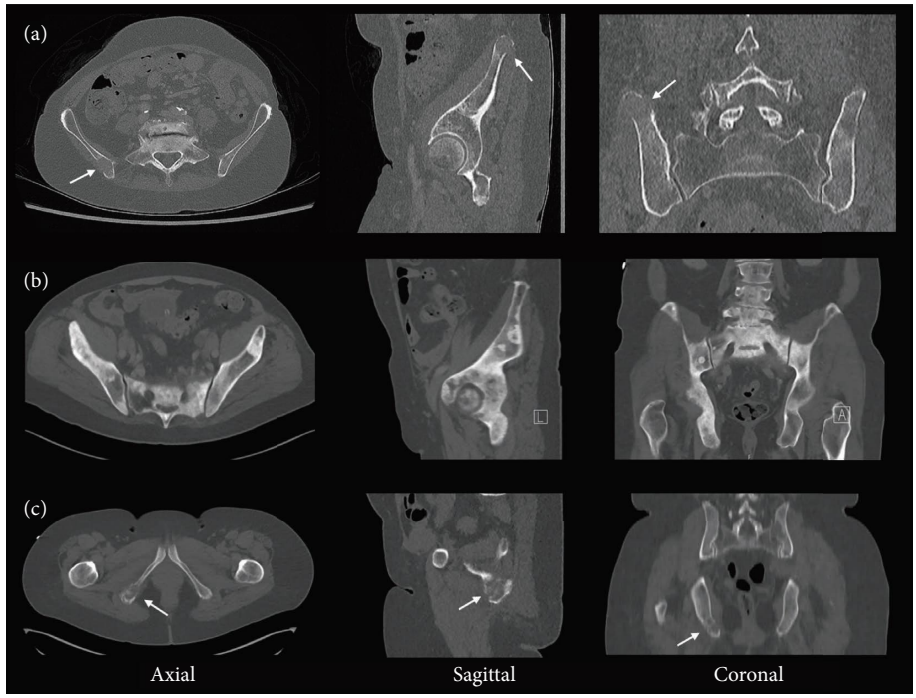

FIGURE 2: Example axial, sagittal, and coronal slices of CT scans from three patients screened for eligibility for magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) treatment of painful nonspinal bone metastases in the pelvic bones. (a) A patient with a painful bone lesion posterior in the right iliac bone (white arrow), deemed eligible for MR-HIFU treatment. (b) A patient ineligible for MR-HIFU treatment due to advanced disease in the pelvic bones. (c) A patient ineligible for MR-HIFU treatment due to a pathological fracture posterior in the right ischial bone (white arrow).

less prevalent), while in other countries, the current population may represent the appropriate group. Second, the pain must be localized, as MR-HIFU is a precision therapy aimed at a specific target lesion. Similar to the first concept, technological advancements could expand the amount of lesions that can be effectively targeted (reducing the amount of patients in 'too extensive/advanced' and 'not accessible by MR-HIFU'), and hence increase the number of patients deemed eligible for MR-HIFU.

An alternative approach that could address all three concepts simultaneously is the use of MR-HIFU as an addition to EBRT. For instance, patients with lymphoproliferative disorders (in whom EBRT is typically highly effective) were excluded upfront in the current study, but they might benefit from the combination of MR-HIFU and EBRT to enhance pain palliation [40]. Other groups that might benefit from the combination of MR-HIFU and EBRT include patients with radio resistant tumors, such as melanoma or renal cell carcinoma (which respond less effectively to EBRT), patients with high pain scores (where maximizing efforts to achieve a rapid and effective pain response is needed), and patients referred for re-irradiation (where effectiveness of EBRT is known to be reduced) [9, 41]. It is also important to note that while complete ablation might not be possible for large lesions or advanced disease spread, partial treatment could still provide symptomatic relief [30]. MR-HIFU could target specific pain-generating areas complementing EBRT on the whole field. Since 'too extensive/advanced' is the largest ineligibility group in the current study, this potentially increases the number of eligible patients for MR-HIFU.

Taken together, patients presenting with small, localized lesions in nonspinal regions, primarily seeking pain relief without additional treatment goals are the most promising candidates for this therapy. These four criteria—lesion size, lesion location, treatment intent, and pain score—are relatively simple, rapid, and straightforward to assess. As a result, approximately 65% of patients are excluded from consideration, leaving only 35% of patients requiring more in-depth screening for eligibility. Moreover, the integration of artificial intelligence (AI) could significantly enhance this process by automatically evaluating the location of the metastasis (spinal vs. nonspinal) and assessing disease extent. For clinical practice, the implementation of such AI would not only reduce the number needed to screen, but also increase the likelihood of identifying eligible candidates within the screened patients, ultimately saving substantial time.

We observed substantial differences in the proportion of eligible patients across institutions (ranging from 4% to 30%). Differences in screening strategies, pain management approaches, and the frequency of referrals for radiotherapy in cases of painful bone metastases among different countries likely contributed to these observed differences [37, 39]. Moreover, differences in patients referred to the participating centers (academic center vs. peripheral center), but also preselection processes in some institutions have led to diverse

Table 3: Results of the detailed analysis of all factors determining eligibility for MR-HIFU in 30 random ineligible patients.

		Center A													Center C											Center D					
Patient-related factors	Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Curative treatment intent		—	—	—	**✓**	—	—	—	—	—	—	—	—	—	—	✓	✓	—	—	—	**✓**	—	—	—	—	—	—	**✓**	—	—	**✓**
Poor condition		?	✓	—	—	—	—	—	—	—	✓	—	—	✓	—	—	—	—	—	**✓**	—	—	—	—	—	—	—	—	**✓**	—	—
Contra-indication for MRI		—	—	—	—	—	—	—	—	—	—	—	✓	—	—	—	—	—	✓	—	—	—	—	—	—	—	—	—	?	—	—
Cognitive impairment		✓	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Afraid of MRI/hospital		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Lesion-related factors		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Too extensive/advanced		—	**✓**	**✓**	—	—	✓	**✓**	—	—	**✓**	✓	**✓**	**✓**	—	—	—	—	**✓**	✓	—	✓	**✓**	—	**✓**	—	—	—	✓	**✓**	—
(Impending) pathological fracture		**✓**	—	—	—	—	—	?	—	—	—	✓	—	—	✓	—	—	—	—	—	—	—	—	—	—	✓	✓	—	—	?	—	—
No moderate/severe pain		?	—	—	✓	—	**✓**	?	—	?	—	**✓**	—	—	**✓**	**✓**	**✓**	**✓**	—	—	✓	—	?	—	—	—	?	?	?	—	?
No cortical involvement		—	—	—	✓	—	—	—	—	**✓**	—	—	✓	—	—	✓	—	—	—	—	—	✓	—	—	—	—	—	—	—	—	—
Not accessible by MR-HIFU		✓	✓	—	—	—	✓	—	✓	—	✓	—	—	—	—	—	—	—	—	—	—	✓	✓	—	✓	**✓**	✓	—	—	—	—
Post operative EBRT		—	—	—	—	—	—	—	—	—	—	✓	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Nerve involvement		—	—	—	—	—	✓	—	**✓**	—	?	—	—	—	—	—	—	—	—	—	—	—	—	—	—	✓	**✓**	—	—	—	—
Not safe to treat with MR-HIFU		—	—	—	—	**✓**	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Other reasons		✓	—	—	—	—	—	—	—	—	—	—	—	✓	—	—	—	—	—	—	—	✓	—	—	—	—	—	—	—	?	—
Local control		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	✓	✓	—	—	—
Screening failure		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
No clear lesion on imaging		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	✓	—	—	—	—	—	—	—	—	—
Soft tissue involvement		—	—	—	—	✓	—	—	✓	—	—	—	—	✓	—	—	✓	—	—	✓	✓	—	✓	**✓**	✓	—	—	✓	—	—	✓

Note: ✓ = ineligible based on that criteria, ? = unclear. The bold **✓** represent the primary reason for ineligibility as used in the primary analysis.
Abbreviations: EBRT = external beam radiotherapy, MR-HIFU = MR-guided high intensity focused ultrasound.

screening populations between the different institutions. In addition, the screening process itself was conducted by the local teams on duty, and thus varied from day to day, from observer to observer, and from one institution to another.

The inherent differences in screening populations and screening methods stem from the nonstandardized approach of this eligibility study. Standardized screening processes with clear, universally applied eligibility criteria would address this. However, the current approach gives valuable insights into the real-world clinical practice, and applying strict eligibility criteria would not fully address the issue due to the uniqueness of each case. Lau et al. also stated that eligibility screening for MR-HIFU treatment should be tailored to individual cases rather than applying (too strict) general criteria [30]. In this context, we performed a deep-dive analysis into 30 randomly selected ineligible patients of our population. Among this subgroup, 27 out of 30 lesions were excluded based on multiple criteria. This implies that addressing one single criterion would typically not be enough to render the lesion eligible. Furthermore, we found a great diversity in ineligibility criteria. Although this random subsample is relatively small and subject to selection bias, these results illustrate the heterogeneity within the patient population and emphasize the need for a patient-specific screening procedure.

The pragmatic design of this study provides helpful insights into daily practice, but also entails a few limitations. First, Radiotherapy Department perspective was chosen, while several other perspectives, such as Oncology or Radiology Department, could have been chosen as well. Because of the study perspective chosen, patients who could not undergo radiotherapy, but who might benefit from MR-HIFU, were out of scope. This is, however, a promising population in which MR-HIFU could be considered. For patients who have already received a toxic dose of EBRT or patients with localized EBRT-refractory painful bone metastases, MR-HIFU could potentially serve as a feasible alternative [19, 21]. Second, the study population consisted of individuals who were referred for EBRT, but not necessarily have actually undergone (local) treatment. As a consequence, we do not know the proportion of patients in which MR-HIFU treatment could serve as an alternative to delivered EBRT treatment. It is fair to expect that this proportion will exceed the reported 8% of the EBRT referrals. Third, some exclusion criteria were study-related and not necessarily strict exclusions for the MR-HIFU treatment itself as we conducted this study as part of the FURTHER trial. For example, there is no firm upper limit to lesion size in clinical practice as long as the lesion is sufficiently approachable; patients with low pain scores are not necessarily ineligible, and patients that cannot or do not want to undergo radiotherapy are not represented in this study. Fourth, this study assumes a sequential screening process (patient level first, lesion level second) implying that no patient-related ineligibility factors could be present in the lesion screening group. Fifth, in this pragmatic study, we did not collect demographic data, such as age, sex, and primary tumor type, of the included and/or eligible patients. This, however, would give additional insights into the group of patients being eligible for MR-HIFU. Future studies should strive to investigate the potential of MR-HIFU as a treatment option for painful bone metastases in a broader range of patients, and to identify the characteristics of the eligible patients. Therefore, the FURTHER trial currently includes an additional patient registry arm to help identify the role of MR-HIFU in some of these subgroups of patients [35].

5. Conclusions

In conclusion, in current clinical practice, only 8% of all lesions referred for EBRT would be eligible to undergo MR-HIFU as alternative treatment. Patient-related as well as technical factors, including need for curative treatment, large lesion size and (impending) pathological fracture, were important drivers of the high ineligibility rate. Substantial differences in eligibility rates among institutions were observed, primarily due to differences in patient populations, referral patterns, and local screening approaches. The variations among centers illustrate the heterogeneity within the patient population, and the wide range of ineligibility criteria emphasizes the need to evaluate each patient's eligibility individually. The use of four simple criteria—lesion size, lesion location, treatment intent, and pain score—could efficiently identify clearly ineligible patients in clinical practice, reducing the number of patients requiring detailed screening. Further investigation into areas such as MR-HIFU as a combination treatment, the effectiveness of partial treatment, and technological advancements hold promise for optimizing its palliative use in bone metastasis patients. Additionally, exploring alternative treatment goals and long-term effects of MR-HIFU, broader patient groups such as studies beyond patients referred for EBRT, and an in-depth analysis of the characteristics of eligible patients will further enhance our understanding of MR-HIFU's clinical potential.

Data Availability Statement

The data that support the findings of this study will be available from the corresponding author upon reasonable request 2 years after the FURTHER trial will be completed.

Consent

No patient consent was required for this study, as only anonymized reasons for ineligibility were recorded as part of routine clinical practice. No identifiable patient data were collected or used for publication purposes.

Conflicts of Interest

The authors declare potential conflicts of interest to the research presented in this paper. Some authors involved in this work received research grants or contracts from Elekta, Dutch Research Council Horizon Europe, Dutch Cancer Foundation, IGEA, Janssen. The authors also have research collaborations with Insightec, Profound, and Philips. The authors affirm their commitment to maintaining research

integrity and impartiality in presenting the findings of this study.

Funding

Financial support was provided by European Union's Horizon 2020 Research and Innovation Program [grant agreement 825859].

Acknowledgments

We thank all partners of the FURTHER consortium.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. *(Supporting Information)*

Supporting Table 1: Clarification and justification of the eligibility criteria for MR-HIFU treatment in patients having painful nonspinal bone metastases.

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