Health economic aspects to the adoption of magnetic resonance image-guided high-intensity focused ultrasound for painful bone metastases

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to my family, for being shore,

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Summary

Bone metastases is a common consequence of advanced cancer that is usually associated with pain, impaired mobility, and reduced overall quality of life. External Beam Radiotherapy (EBRT) is the current standard of care; however, it might take four weeks to induce pain relief. Moreover, 50% of patient recur pain after initial response to EBRT, and reirradiation is limited due to the risk of cumulative doses harming surrounding structures. Magnetic Resonance image-guided High-Intensity Focused Ultrasound (MR-HIFU) is an emerging non-invasive procedure that can provide significant and rapid pain palliation for patients with bone metastases with a favorable safety profile. Thus, the FURTHER project aims to evaluate the effectiveness of MR-HIFU to pain palliation of painful bone metastases compared to the EBRT in a randomized controlled trial. In addition to evidence on effectiveness of MR-HIFU, health economic evidence was needed to support adoption of MR-HIFU in Europe.

This cumulative dissertation comprises three dissertation subprojects. The first subproject describes a time-driven activity-based costing approach to determine the costs of the MR-HIFU from the hospital perspective. The second subproject consists of an early economic modelling study that aimed to evaluate the cost-effectiveness of MR-HIFU compared to EBRT from the perspective of the German Statutory Health Insurance (SHI). The third subproject consists of a mixed-method participatory research with the objective to investigate contextual factors influencing the adoption of MR-HIFU for treatment of bone metastases in Europe.

Based on results of the three subprojects, three main conclusions follow. First, adoption of MR-HIFU would benefit greatly from improvements to the care pathway, which would reduce costs of MR-HIFU, and subsequently impact the cost-effectiveness in relation to EBRT. Second, although still in early phase of implementation, MR-HIFU is potentially cost effective for patients with bone metastases and further research is worthwhile to better inform the decision whether to adopt MR-HIFU as a treatment alternative in the German SHI. Third, to ensure successful adoption of MR-HIFU, several contextual factors have to be addressed strategically, such as hospital referral, logistics and patients' preferences.

MR-HIFU is a promising treatment strategy for patients with painful bone metastases. Although clinical evidence on the effectiveness of MR-HIFU is still needed, the health economic evidence generated in this cumulative dissertation provides strong impetus for the adoption of MR-HIFU in clinical practice.

Zusammenfassung

Knochenmetastasen sind eine häufige Begleiterscheinung bei Krebs im fortgeschrittenen Stadium. Sie führen häufig zu Schmerzen, eingeschränkter Mobilität und einer verringerten allgemeinen Lebensqualität. Der aktuelle Behandlungsstandard ist die Strahlentherapie (EBRT). Schmerzlinderung tritt jedoch häufig erst 4 Woche nach der Bestrahlung ein. Darüber hinaus treten bei 50% der Patienten nach EBRT erneut Schmerzen auf. Eine erneute Bestrahlung ist häufig nicht möglich, da die Schäden an den umgebenden Strukturen und Gewebe durch die Höhe der kumulativen Strahlendosis berücksichtigt werden muss. Magnetresonanzgesteuerte hochintensive fokussierte Ultraschalltherapie (MR-HIFU) ist ein nicht-invasives Verfahren, das eine signifikante und schnelle Schmerzlinderung für Patienten mit Knochenmetastasen mit einem günstigen Sicherheitsprofil bieten kann. Das FURTHER-Projekt zielt darauf ab, die Wirksamkeit von MR-HIFU zur Linderung schmerzhafter Knochenmetastasen im Vergleich zur EBRT in einer randomisierten kontrollierten Studie zu bewerten. Zusätzlich zum Nachweis der Wirksamkeit von MR-HIFU waren gesundheitsökonomische Nachweise erforderlich, um die Einführung von MR-HIFU in Europa zu unterstützen.

Diese kumulative Dissertation umfasst drei Dissertationssubprojekte. Das erste Subprojekt beschreibt einen Prozesskostenrechnungsansatz zur Ermittlung der Kosten des MR-HIFU aus Krankenhaussicht. Das zweite Subprojekt besteht aus einer frühen ökonomischen Modellierungsstudie, die darauf abzielte, die Kosteneffektivität von MR-HIFU im Vergleich zu EBRT aus Sicht der deutschen gesetzlichen Krankenversicherung (GKV) zu bewerten. Das dritte Subprojekt besteht aus einem Mixed-Methods Ansatz mit dem Ziel, Kontextfaktoren zu untersuchen, die die Einführung von MR-HIFU zur Behandlung von Knochenmetastasen in Europa beeinflussen können.

Aus den Ergebnissen der Subprojekte ergeben sich drei Hauptschlussfolgerungen. Erstens eine Verbesserung im Versorgungspfad ist wünschenswert, und die daraus resultierende Kostensenkung würde sich anschließend auf die Kosteneffektivität in Bezug auf EBRT auswirken. Zweitens ist MR-HIFU, obwohl es sich noch in einer frühen Phase der Implementierung befindet, potenziell kosteneffektiv für Patienten mit Knochenmetastasen. Weitere Forschung ist lohnenswert, um die Entscheidung zu unterstützen, ob MR-HIFU als Behandlungsalternative in den Behandlungskatalog der deutschen GKV eingeführt werden soll. Drittens sollten für eine erfolgreiche Einführung von MR-HIFU mehrere Kontextfaktoren strategisch angegangen werden, wie beispielweise Krankenhauslogistik und Patientenpräferenzen.

MR-HIFU ist eine vielversprechende Behandlungsstrategie für Patienten mit schmerzhaften Knochenmetastasen. Obwohl noch klinische Beweise für die Wirksamkeit von MR-HIFU benötigt werden, liefern die in dieser kumulativen Dissertation generierten gesundheitsökonomischen Ergebnisse einen starken Impuls für die Einführung von MR-HIFU in der klinischen Praxis.

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List of Abbreviations

BPI	Brief Pain Inventory
BTA	Bone Targeting Agents
CCR	Capacity Cost Rate
CIBP	Cancer-induced Bone Pain
DRG	Diagnosis-Related-Groups
EBRT	External Beam Radiotherapy
ESTRO	European Society for Radiotherapy and Oncology
EVPI	Expected Value of Perfect Information
EVPPI	Expected Value of Perfect Partial Information
FURTHER	Focused Ultrasound and RadioTHERapy for Noninvasive Palliative Pain Treatment in Patients with Bone Metastases
GCM	Group Concept Mapping
Gy	Gray (International system unit of radiation dose)
HIFU	High-Intensity Focused Ultrasound
ICER	Incremental Cost-Effectiveness Ratio
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*
MRI	Magnetic Resonance Imaging
MR-HIFU	Magnetic Resonance Image-guided High-Intensity Ultrasound
NUB	*neue Untersuchungs- und Behandlungsmethoden*
NRS	Numeric Rating Scale
OMED	Oral Equivalent Daily Morphine use
OPS	*Operationen- und Prozedurenschlüssel*
QALY	Quality-Adjusted Life Year
R&D	Research and Development
RCT	Randomized Controlled Trial
SAVI	Sheffield Accelerated Value of Information
SHI	Statutory Health Insurance
SRE	Skeletal-Related Events
TDABC	Time-driven activity-based costing
T	Tesla (unit of magnetic flux density)
UHC	University Hospital of Cologne
U.S.	United States
U.K.	United Kingdom
VOI	Value of Information
WHO	World Health Organization
WTP	Willingness-To-Pay

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Introduction

Advances in cancer care led to a decline in cancer-related mortality worldwide (Hashim et al., 2016). As cancer patients live longer, palliative care has become an important therapy goal, driving innovation to alleviate the debilitating complications that accompany advanced cancer, such as bone metastases. However, to incorporate innovative medical technologies within new and emerging care pathways, several challenges must be overcome. In addition, the increase in health expenditure related to new technologies raises concerns about affordability and sustainability of healthcare systems. Hence, this cumulative dissertation aims to provide health economic evidence to inform the adoption of a new intervention for pain palliation of patients with uncomplicated bone metastases: the Magnetic Resonance Image-guided High-Intensity Ultrasound (MR-HIFU).

Although this cumulative dissertation focusses on health economic aspects of MR-HIFU, an overview of the clinical rationale and evidence is required to properly understand the application of MR-HIFU for bone metastases:

Chapter I is divided in three sections. The first section is dedicated to introducing the patient population to whom the intervention is targeted. To depict this patient population, the epidemiology of bone metastases, the mechanisms of cancer-induced bone pain and the clinical characteristics of bone pain in cancer patients is described. The second section offers an overview of the clinical management of bone metastases. The intention is to summarize the main pillars of clinical management and to place the intervention within the broader clinical practice. The main concepts in palliative treatment of bone metastases are summarized, with focus on external beam radiotherapy (EBRT) as the current standard of care for uncomplicated painful bone metastases. The third section introduces the intervention under study, MR-HIFU. Based on a narrative literature review on the effectiveness and safety of MR-HIFU for bone metastases, this session presents the basic principles of HIFU therapy and the main steps of the procedure; and current clinical evidence on MR-HIFU for bone metastases.

Finally, the FURTHER (Focused Ultrasound and RadioTHERapy for noninvasive palliative pain treatment in patients with bone metastases) project is presented. The FURTHER project is funded by the European Commission's research and innovation program horizon 2020 (grant agreement No 825859). This cumulative dissertation was conducted in the context of the FURTHER project but did not use clinical data from the main randomized controlled trial (RCT).

Chapter II presents the relevance of health economics and the need for health economic evidence for the adoption of MR-HIFU for bone metastases. In addition, the overall aim of this cumulative dissertation, and specific objectives of the dissertation subprojects I, II and III are introduced.

Chapter III presents a summary of each dissertation project, including methodology and key findings. The dissertation subprojects are reproduced in full in *chapter IV* (subproject I), *chapter V* (subproject II) and *chapter VI* (subproject III). *Chapter IV* contains the research published in the International Journal of Hyperthermia, entitled: Time-driven activity-based costing (TDABC) approach of MR-HIFU for painful bone metastases (Simões Corrêa Galendi, Yeo, Simic, et al., 2022). *Chapter V* contains the research published in Frontiers in Oncology, entitled Early Economic Modeling of MR-HIFU compared to radiotherapy for pain palliation of bone metastases (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). *Chapter VI* reproduces the research published in the International Journal of Environmental Research and Public Health, entitled: Factors influencing the adoption of MR-HIFU for painful bone metastases in Europe, a Group concept mapping study (Simões Corrêa Galendi et al., 2023).

Chapter VII discusses the methodological strengths and limitations of this cumulative dissertation, the advances on health economics of MR-HIFU for bone metastases and the challenges that lie ahead. The results and conclusions are discussed in relation to the current state of research. In detail, previous applications of TDABC in healthcare and previous cost-effectiveness analyses assessing technologies applied to bone metastases are discussed. Then, a discussion on how contextual factors affect the adoption of healthcare technologies is presented by analyzing an akin situation in the radiotherapy field.

Lastly, the implications for research and practice are discussed, focusing on the practical applications to the FURTHER project and a future trial-based cost-effectiveness analysis using FURTHER RCT data. In addition, the implications to hospital management and technology developers, and for clinical practice are discussed.

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Chapter I

Burden and Palliative Treatment of Bone Metastases

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1. The burden of bone metastases

1.1. Epidemiology of bone metastases

Bone is the third most common site (after the lung and liver) of metastatic disease in patients with cancer (Ryan et al., 2022). A retrospective study using real world data from an oncologic registry in the United States (U.S.) showed that the cumulative incidence of bone metastases within 30 days of the first solid tumor diagnosis increased from 2.9% to 8.4% during a ten-year period (Hernandez et al., 2018). The incidence of de novo bone metastases – that is, patients presenting bone metastases at the time of the primary diagnosis – is 18.8 /100,000 patient-year in the U.S., with variations due to sex, age group, and primary tumor site (Ryan et al., 2022).

Breast, prostate, and lung cancer are more likely to metastasize to the bone than other solid tumors (Gdowski, Ranjan, & Vishwanatha, 2017; Ryan et al., 2022). The cumulative incidence of de novo bone metastases is 7.6% for lung cancer, 1.5% for breast cancer, and 1.7% for prostate cancer (Hernandez et al., 2018). With regard to anatomic location, bone metastases are most often located in the vertebrae (69%), followed by the pelvic bones (41%), long bones (usually the proximal femur) (25%), and skull (14%) (Zajączkowska, Kocot-Kępska, Leppert, & Wordliczek, 2019).

The prognosis of patients with bone metastasis is heterogeneous across different cancer types. According to a Danish population-based cohort study, one-year survival after bone metastasis diagnosis was lowest in patients with lung cancer (10%) and highest in patients with breast cancer (51%) (Svensson, Christiansen, Ulrichsen, Rørth, & Sørensen, 2017). Three-year survival ranged from 2% for lung cancer, 12% for prostate, to 25% for breast cancer (Svensson et al., 2017). Moreover, the prognosis is worse for patients with de novo bone metastases than for those who develop bone metastases later in the course of cancer treatment, and for patients presenting concomitant metastases in other organs (Svensson et al., 2017).

Furthermore, the occurrence of skeletal-related events (SRE) has a strong impact on survival and quality of life. SRE is a combined outcome that includes pathological fractures, radiation to the bone, surgery to the bone, or spinal cord compression. According to German

claims data from 2010 to 2018, 45.2% of 9,832 patients with bone metastases reported experiencing at least one SRE (Hardtstock et al., 2021). Radiation to the bone is the most frequent (66%), while spinal cord compression (7%) and surgery to the bone (10%) are the less common events (Hechmati et al., 2013).

1.2. Clinical burden of bone metastases

Cancer-induced bone pain is a common and devastating symptom for patients with cancer. Approximately 60-84% of patients with advanced cancer are estimated to experience varying degrees of bone pain (Lipton, 2010; Portenoy, 2011; Ripamonti & Fulfaro, 2001). The mechanisms leading to bone pain are complex and evolve with cancer progression (Zajączkowska et al., 2019). Most patients initially experience intermittent dull aches, and as the disease progresses, pain becomes more constant and severe (Zajączkowska et al., 2019), which compromises patients' mobility (Cleeland et al., 2016).

Continued tumor growth within the bone usually leads to breakthrough pain, a transitory flare of pain that occurs on the background of a relatively well-controlled baseline pain (Fallon et al., 2018). Breakthrough pain poses a significant therapeutic challenge because it usually evades the management with opioids and has a negative effect on daily functioning and quality of life (Delaney, Fleetwood-Walker, Colvin, & Fallon, 2008). Besides, there is often a neuropathic component to bone pain since tumor growth can cause compression and damage to the surrounding nervous system structures (Delaney et al., 2008; Zajączkowska et al., 2019). In addition, pathological fractures resulting from metastatic lesions in bone structure can initiate pain or worsen already existing pain (Delaney et al., 2008; Zajączkowska et al., 2019).

1.3. Economic burden of bone metastases

The economic burden of bone metastases in the U.S. in 2004 was estimated at $12.6 billion, corresponding to 17% of the total direct medical costs for cancer treatment (Schulman & Kohles, 2007). For patients with bone metastases, the mean direct medical cost for all types of cancer was $75,329 /patient, compared to $31,382 for cancer patients without bone metastases (Schulman & Kohles, 2007). Healthcare resource utilization and costs incurred by patients with bone metastases are mainly explained by expenses in treating SRE, as demonstrated for many solid tumors (Jayasekera et al., 2014; Lorusso et al., 2014).

According to an analysis based on large claims data from Germany (3.2 million insured persons), SRE are associated with both a significant increase in the average number of hospitalization days and inpatient-care costs. In this analysis, the average cost of patients who experience SRE was €23,689 /patient-year, compared to €20,403 /patient-year for non-SRE patients, resulting in a total cost ratio of 1.16 ($p<0.001$) (Hardtstock et al., 2021). A European

cohort including patients from Germany, Italy, Spain, and the United Kingdom (U.K.), reported similar findings. In this dataset, one of the costliest SREs was surgery to the bone (€3,348 to €9,407 /event), mainly caused by high inpatient costs (Hechmati et al., 2013).

In conclusion, advances in oncologic treatments and earlier diagnosis have extended survival of patients with advanced cancer (von Moos, Sternberg, Body, & Bokemeyer, 2013). However, extending survival also prolongs the course of the disease and its associated sequelae. Therefore, palliative treatment of bone metastases has become an important therapy goal, to reduce not only the burden to the patient, but also the societal and economic burden of bone metastases in oncologic care.

2. Palliative treatment of painful bone metastases

2.1. Palliative treatment of uncomplicated painful bone metastases

The palliative treatment of uncomplicated bone metastases (i.e., those without pathological fracture or spinal cord compression) has primarily two goals: symptom management and prevention or delay of SRE (Fallon et al., 2018; Hechmati et al., 2015; Qian et al., 2018).

First and foremost, bone targeting agents (BTA) should always be considered in the therapeutic regimen for patients with bone metastases, especially for patients with good prognosis to prevent SRE (Fallon et al., 2018). Bisphosphonates such as pamidronate or zoledronic acid, or the monoclonal antibody denosumab have shown to reduce osteolytic lesions (Machado, Cruz, Tannus, & Fonseca, 2009; Menshawy et al., 2018). Strong evidence supports the effectiveness of BTAs to prevent pathological fractures, and they might even have slight analgesic effect (Jakob et al., 2022; Machado et al., 2009; Menshawy et al., 2018).

Nevertheless, opioids are the mainstay of analgesic therapy. A traditional approach to analgesic therapy was proposed by the World Health Organization (WHO). According to this approach, patients receive a sequential three-step ladder including weak and strong opioids depending on pain intensity (Anekar & Cascella, 2022). The optimal dosage should be titrated to achieve adequate pain relief without unacceptable adverse effects (Anekar & Cascella, 2022).

Adverse effects from opioid therapy are common. They include bowel dysfunction (e.g., constipation, bloating, incomplete evacuation, and gastric reflux), nausea, vomiting, pruritus, respiratory depression, and central nervous system toxicities (drowsiness, cognitive impairment, confusion, hallucinations, myoclonic jerks and more rarely, opioid-induced hyperalgesia (Fallon et al., 2018). To reduce the incidence and the severity of adverse effects, a dose reduction combined with alternative co-analgesic strategies are recommended (Anekar & Cascella, 2022).

Local treatments such as EBRT and ablation techniques are often applied as co-analgesic strategy (Fallon et al., 2018). Conventional EBRT is the treatment of choice for uncomplicated painful bone metastases, especially if pain is not sufficiently controlled by pain medication or when a reduction of pain medication is desired (van der Velden et al., 2022). Figure 1 summarizes the main pillars of clinical management and illustrates the place of EBRT within the broader clinical practice.

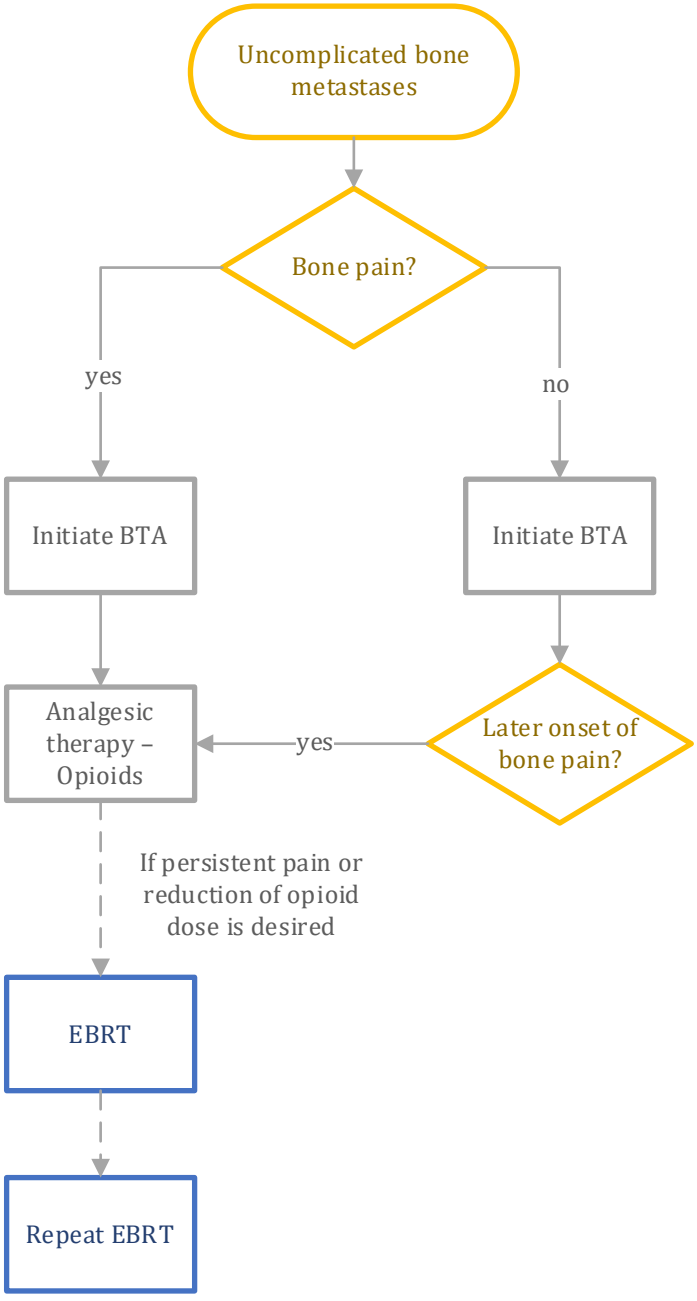

Figure 1. Role of External Beam Radiation Therapy in the management of uncomplicated bone metastases. Abbreviations. BTA: Bone targeting agents, EBRT: External Beam Radiation Therapy.

2.2. EBRT for uncomplicated painful bone metastases

EBRT is a frequently used modality for bone metastases, because of its effectiveness for pain palliation and for causing local tumor control (i.e., tumor shrinkage or growth inhibition). Approximately 60-70% of patients initially respond to EBRT over the course of four weeks following treatment, with complete pain relief in one-third of patients (Jones, Lutz, Chow, & Johnstone, 2014; van der Linden et al., 2004; Westhoff et al., 2015). EBRT can be delivered in single-fraction of eight Gray (Gy) or multi-fraction schedules (e.g. 20 Gy in five fractions, 24 Gy in six fractions or 30 Gy in ten fractions) (Leitlinienprogramm Onkologie, 2017; Lutz et al., 2017). In Europe, data from 2004 to 2011 showed that 50.5% of patients were treated with single-fraction, and 20Gy in five fractions was the most common multi-fraction scheme (23%), followed by schemes with ten or more fractions (12.3%) (Spencer et al., 2015).

A meta-analysis based on 25 RCTs including 5,617 patients has shown equivalent pain relief following single-fraction compared to various multi-fraction schemes for patients with painful uncomplicated bone metastases (Rich et al., 2018). Although the duration of pain palliation is likewise similar in single-fraction and multi-fraction EBRT, the retreatment rate after multi-fraction EBRT is reported at 8%, and that after single-fraction is 20% (Rich et al., 2018). The retreatment rate after multi-fraction EBRT is lower, probably due to concerns with the cumulative radiation dose rather than due to a greater need of retreatment (van der Linden et al., 2004; Yarnold, 1999).

Adverse events such as itching, skin reactions and tiredness are usually manageable. The most common adverse events are gastrointestinal symptoms (Sze, Shelley, Held, & Mason, 2004); about 40% of patients treated with EBRT need symptomatic medication for nausea and vomiting for the first two weeks following treatment (Yarnold, 1999). Moreover, an initial flare in bone pain is common, but can be managed with dexamethasone alongside analgesics (Fallon et al., 2018).

The risk of a pathological fracture on the treated site following conventional EBRT techniques is below 5% (Rich et al., 2018). A recent meta-analysis of RCTs comparing fractionation schemes showed that single-fraction is associated with a slightly higher but non-significant fracture rate compared to multi-fraction schemes (OR: 1.2, 95% CI 0.72 – 1.98) (Rich et al., 2018).

Although EBRT is a well-stablished treatment option for patients with uncomplicated bone metastases, supported by consistent medical evidence, there is still an unmet need. Among patients initially responding to EBRT, about 50% experience recurrent pain (Huisman et al., 2012). For those non-responding to EBRT or suffering recurrent bone pain, the option of re-irradiation is limited because cumulative radiation doses might be harmful for organs surrounding the target lesion. According to clinical evidence, only 58% of patients undergoing re-

irradiation benefit from it (Huisman et al., 2012). Moreover, pain relief after EBRT might take up to four weeks, and for patients with limited life expectation, a more rapid pain relief would be beneficial.

3. The intervention

3.1. High-intensity focused ultrasound (HIFU)

HIFU ablation is a promising technique for patients with cancer-induced bone pain. Acoustic energy of HIFU systems determines a temperature rise (at a thermal threshold of 65 to 85 °C depending on the tissue absorption coefficient) in biological tissues, leading to coagulative necrosis on the treated target area (Scipione et al., 2018). There are multiple mechanisms that can explain the effects of HIFU in terms of pain relief, including periosteum denervation, tumor debulking (with reduction in the pain related to the expansion of the mass), and the reduction of chemical mediators' release and the degree of osteoclast-mediated osteolysis (Dababou et al., 2018; Yeo, Elevelt, et al., 2015). Pre-clinical studies have shown that HIFU ablations induced bone damage at the cellular level, thereby triggering bone repair and modelling, without compromising the mechanical function of the bone or causing micro-cracks at the bone tissue level (Yeo, Arias Moreno, et al., 2015).

HIFU treatment can be guided by magnetic resonance imaging (MRI): magnetic resonance imaging-guided high-intensity focused ultrasound (MR-HIFU). The contrast resolution of MRI allows a reliable target delineation and MRI thermometry provides a real-time temperature assessment of thermal-dose distribution on surrounding soft tissues (Scipione et al., 2018). Hence, the treatment can be modulated according to thermal feedback: acoustic energy can be increased or decreased accordingly if the temperature rise is insufficient or excessive.

3.2. Effectiveness and safety of MR-HIFU for bone metastases

There is growing evidence on the effectiveness and safety of MR-HIFU for uncomplicated bone metastases. The largest randomized sham-controlled trial to date included 112 patients and demonstrated that MR-HIFU provided pain relief at three days after treatment, and up to three months of follow up. The response rate for the primary endpoint (improvement in self-reported pain) was 64% in the MR-HIFU arm compared to 20% in the sham arm ($P < .001$) (Hurwitz et al., 2014). Among the responding patients in the MR-HIFU treated group, 27% reported discontinuation of pain medication, and 17% required less medication compared to baseline (Hurwitz et al., 2014).

A recent proportional systematic review included three randomized clinical trials, six retrospective and 24 prospective studies, synthesizing results for 1,082 patients. In the meta-

analysis, the pooled proportion of overall treatment response was 79% (95% CI: 73–83%, I^2: 39%, 20 studies, 636 patients) (Baal et al., 2021). These results were confirmed by a second systematic review and meta-analysis, which included only studies with at least ten patients (Han, Huang, Meng, Yin, & Song, 2021). Han et al. divided treatment response in two categories: complete response if the final pain score was zero (i.e., measured on a scale from zero to ten, the latter being the higher intensity in pain), and partial response if there was any reduction in the pain score or in the opioid dose. Among patients included in this meta-analysis, 36% had a complete response after treatment with MR-HIFU (95% CI: 24-48%, I^2:71%, 11 studies, 256 patients), and 47% had partial response (95% CI: 36%–58%, I^2:64.7%, 11 studies, 256 patients) (Han et al., 2021).

According to the meta-analyses by Han et al., MR-HIFU leads to a gradual decrease in pain score. Compared with baseline, at 0–1 week there was a reduction of 2.54 in mean pain scores (95% CI: 1.92–3.16, $p < 0.01$). At 1–5 weeks, pain was further improved with a mean reduction in pain score of 3.56 (95% CI: 3.11–4.02, $p < 0.01$); and a significant pain improvement at 5–14 weeks, with a mean reduced pain score of 4.22 (95% CI: 3.68–4.76, $p < 0.01$) (Han et al., 2021).

Compared with EBRT, MR-HIFU showed a similar overall treatment response rate but faster pain relief in a single-centre matched-pair study (pain relief in 71% vs. 26% at one week, $p = 0.0009$ and 81% vs. 67% at one month, $p = 0.3753$) (Lee et al., 2017). These results were confirmed in a recent prospective non-randomized phase II study comparing MR-HIFU with EBRT: pain relief in MR-HIFU group occurred in 91% vs 67% in the EBRT group at one-month follow-up ($p < .001$, 198 patients), and was sustained in a 12-month follow-up (Napoli et al., 2023).

Finally, MR-HIFU has a favourable safety profile (Huisman et al., 2015). Among 799 patients across 26 studies included in the systematic review from Baal et al, approximately 12% of the patients experienced sonication-related pain during MR-HIFU treatment, which was usually resolved within one day (Baal et al., 2021). Other minor adverse events that occurred even less often are grade I skin burn (Li et al., 2010), limb numbness (Gu et al., 2015), and grade II myositis (Lee et al., 2017). Serious adverse events were reported by the largest placebo controlled RCT, including two fractures (one outside the treated area), one case of grade III skin burn (associated with protocol deviation) and one case of hip flexor neuropathy (Hurwitz et al., 2014). Moreover, one case of deep vein thrombosis has been reported (Baal et al., 2021).

MR-HIFU can be offered as first-line treatment, but most of the available evidence was gathered from patients who received MR-HIFU after at least one course of EBRT, or even after exhausting maximal EBRT possibilities (Huisman et al., 2015). Notably, some case series indicate that patients without prior EBRT might respond better to MR-HIFU than those with prior radiation (response rate of 87% vs. 69%) (Baal et al., 2021; Pfeffer et al., 2014). The combination

of single-fraction EBRT followed by MR-HIFU within four days has been tested in a feasibility study with six patients, and no serious adverse events occurred (Bartels et al., 2021). Combining MR-HIFU with EBRT may result in an improved pain response as compared to what each single treatment may achieve since both treatments have slightly different mechanisms of action (Bartels et al., 2021; Huisman et al., 2015).

Although early evidence is promising, the role of MR-HIFU as first-line treatment for painful bone metastases has not yet been determined due to lack of a RCT comparing MR-HIFU with the current standard of care, EBRT. Box 1 summarizes the clinical rationale leading to the application of MR-HIFU for bone metastases.

Box 1. Key points on the application of MR-HIFU for bone metastases

- Bone metastases is a common consequence of advanced cancer that is usually associated with pain, impaired mobility, and reduced overall quality of life.
- Opioids are regularly used in the baseline pharmacologic treatment for pain palliation. However, high doses required to manage pain effectively are associated with numerous adverse effects. Thus, co-analgesic strategies are often needed.
- EBRT is the current standard of care for patients with uncomplicated bone metastases, but 30-40% of patients do not have significant improvement in pain, and re-irradiation is limited due to concerns with the cumulative dose.
- MR-HIFU is an emerging non-invasive procedure that is able to provide significant and rapid pain palliation for patients with bone metastases with a favorable safety profile.

3.3. The FURTHER project

The FURTHER project consists of a multicenter three-armed RCT, performed in six hospitals in four European countries: Germany, Italy, the Netherlands, and Finland (ClinicalTrials.gov registration number NCT04307914). The FURTHER consortium started including patients on 10.03.2020. Because of the COVID pandemic, recruitment stopped for almost two years and is still ongoing.

The study population includes male and female adults (age ≥ 18 years) with non-vertebral painful bone metastases, who have a solitary painful metastatic bone lesion or multiple metastatic lesions with one predominantly painful target lesion (two points or higher pain score than other lesions). Exclusion criteria are patients with (impending) pathological fractures or neurological symptoms due to nerve involvement of target lesion (Slotman et al., 2022).

Patients (n=216) are randomized in a 1:1:1 ratio to one of the three intervention arms, and either receive standard EBRT treatment, MR-HIFU only treatment, or combined EBRT and MR-HIFU treatment (Figure 2). Randomization, stratified by institution and planned EBRT fractionation schedule, is done at the study site, by a computer-generated sequence using variable block randomization method (Slotman et al., 2022).

MR-HIFU treatment is delivered on a clinical MR-HIFU system integrated into a 1.5 or three Tesla (T) MR scanner. The EBRT schedule is at the discretion of the treating radiation oncologist (i.e., single-fraction, or a multi-fraction regime of 20 Gy in five fractions, 24 Gy in six fractions or 30 Gy in ten fractions). Patients and doctors are not blinded to treatment and treatment allocation is not concealed (Slotman et al., 2022).

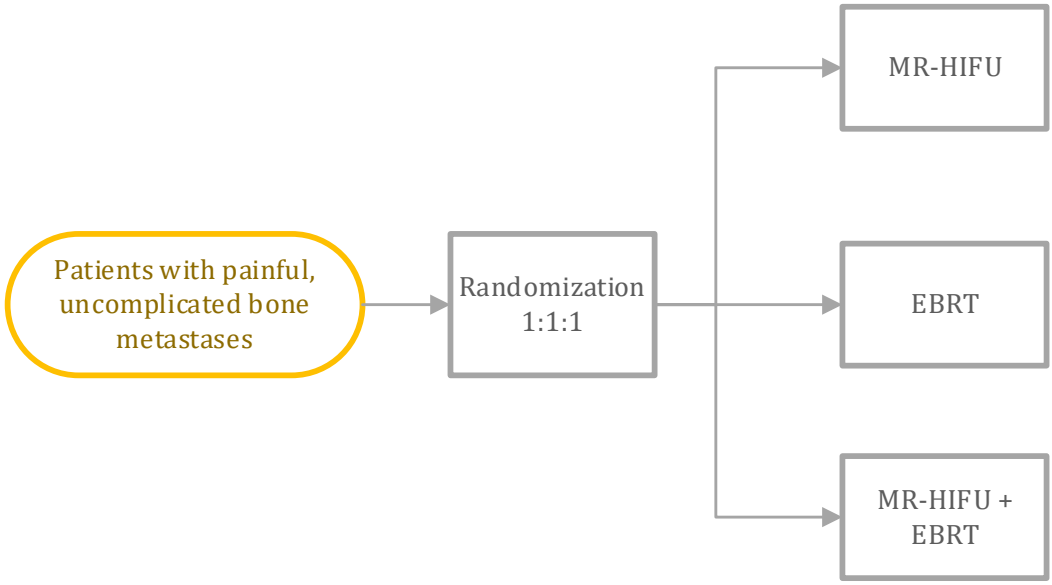

Figure 2. Flowchart of the FURTHER-trial randomization design. Adapted from Slotman et al., 2022. Abbreviations. MR-HIFU: Magnetic Resonance Image-guided High-Intensity Focused Ultrasound. EBRT: External Beam Radiation Therapy.

The primary outcome is patient reported pain response 14 days after completion of treatment. Pain response is based on the numeric rating scale (NRS) and the pain severity index calculated from the brief pain inventory (BPI) questionnaire (Wu, Beaton, Smith, & Hagen, 2010). In addition, analgesic drug use is recorded, alongside the oral equivalent daily morphine use (OMED). Following the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases, pain is assessed by the worst pain score over the previous three day (Chow et al., 2002). Patients are considered responders when either a reduction of pain score of at least two 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 are categorized as non-responders (Chow et al., 2002).

Secondary endpoints include patient reported pain response at 14 days after inclusion, as this reflects the differences in complexities in planning EBRT versus MR-HIFU (Slotman et al., 2022). Other secondary endpoints include quality of life at one, two and four weeks, and three and six months after treatment (Chow et al., 2009; Groenvold et al., 2006). Finally, secondary endpoints include cost-effectiveness and cost-utility analyses (Slotman et al., 2022).

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Chapter II

The Need for Health Economic Evidence

1. Health economic aspects

1.1. Cost and financing of MR-HIFU

Many European countries (e.g., Germany, the Netherlands, Finland) increasingly move towards payments based on diagnosis-related-groups (DRG) (Tan, 2014). In Germany, reimbursement via DRG-based payments correspond to 80% of hospital expenses (Tan, 2014). The German DRG (gDRG) tariffs are regularly updated based on cost-accounting data collected by participating hospitals.

Innovative medical devices such as MR-HIFU are integrated into the gDRG scheme by adding new codes to the German procedure classification (*Operationen- und Prozedurenschlüssel*), the OPS codes. After the introduction of a new OPS code, the hospitals have to present detailed cost calculation correlating to the application of the respective OPS code in a determined data year. Thus, the time-lag until an innovative technology is integrated in the gDRG scheme may take up to three years (Ex, Vogt, Busse, & Henschke, 2020).

To address this systemic gap in the gDRG system and promote faster adoption of potentially beneficial innovative medical devices, German hospitals can negotiate for additional funding (i.e., innovation payments or *neue Untersuchungs- und Behandlungsmethoden* - NUB) (Allin et al., 2019). The approval of a NUB payment is contingent on the hospital demonstrating that the current gDRG-tariff does not cover the costs for the procedure (Ex et al., 2020). Thus, a cost calculation based on the care pathway and the associated resource consumption is essential to allow fair reimbursement – in early stages to apply for a NUB payment and later to adjust and update the gDRG-tariffs.

An early assessment of costs associated with MR-HIFU treatment is a key element to enable appropriate financing. Additionally, detailed cost-accounting information can support the hospital management in making strategic decisions (Vogl, 2012). As described in chapter I (*session 3.1 High-Intensity Focused Ultrasound*), MR-HIFU procedure is complex because it involves coordination of several hospital structures (e.g., availability of MRI resources and HIFU equipment) and medical teams (e.g., anesthesiologists, radiologists, oncologists). The lack of a

care pathway for MR-HIFU procedure is detrimental to the patients and the medical team, who have to deal with waiting times and logistic difficulties; and to the hospital that cannot underpin the procedure costs to actual resource consumption. Lastly, the cost of MR-HIFU is an important premise for economic evaluations aiming at comparing health outcomes and costs (Huisman et al., 2015).

1.2. Cost-effectiveness of MR-HIFU

When innovative technologies are added to the treatment portfolio, evidence on cost-effectiveness ensures that the available resources in healthcare system are being used as wisely as possible (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015). Cost-effectiveness analyses evaluate the effectiveness of two or more intervention relative to their cost, by calculating the incremental cost-effectiveness ratio (ICER). The ICER is the summary measure representing the economic value of an intervention (A) compared to an alternative (B):

$$ICER = \frac{Cost_A - Cost_B}{Effectiveness_A - Effectiveness_B}$$

To decide whether choosing the intervention is an efficient use of resources, the ICERs have to be compared to a willingness-to-pay (WTP) threshold. The WTP threshold sets the maximum a decision-maker is willing to pay for a unit of health outcome, usually expressed as quality-adjusted life year – QALY (York Health Economics Consortium, 2016b).

Cost-effectiveness analyses are usually undertaken once high-quality clinical evidence is available. As shown in *chapter I* (session *3.2 Effectiveness and safety of MR-HIFU for bone metastases*), to date there is no RCT directly comparing MR-HIFU with EBRT for painful bone metastases. Although an early economic modeling (i.e., based on early evidence) is invariably associated with high uncertainty, being thus unlikely to provide definitive recommendations regarding reimbursement or implementation (Grutters et al., 2019), early economic modeling can serve several purposes, such as:

(i) Distinguishing between innovations with and without potential cost-effectiveness. Early economic modeling can aid manufacturers decide to continue investing in product research and development (R&D) (Grutters et al., 2019). Manufacturers can incur substantial capital losses when evidence generated at later stages deems a technology to be cost-ineffective (and therefore not covered/reimbursed) (Ijzerman & Steuten, 2011). From the payer and hospital perspective, early knowledge on the potential cost-effectiveness of a medical device can justify the early investments, or avoid sunk costs with installation and personnel training (Grutters et al., 2019).

(ii) Informing the value of conducting further research (Ijzerman & Steuten, 2011). Value of information (VOI) analyses based on early economic modeling can identify the parameters that are likely to affect the decision-making. Hence, conducting an early economic modeling before planning or while a clinical trial is in progress can contribute to prioritizing research efforts (York Health Economics Consortium, 2016a).

(iii) Identifying more cost-effective care pathways. Early economic models offer the opportunity to assess how alternative ways of positioning innovative treatments within the care pathway can affect their cost-effectiveness. For instance, even if MR-HIFU is not cost effective compared to EBRT, it may still be valuable if it is offered as add-on to existing treatments or only to specific patient subgroups. Knowledge of exactly how a new technology can best add value can support its future adoption (Grutters et al., 2019).

1.3. Adoption of MR-HIFU

The diffusion of innovations in healthcare is determined by a complex interaction of multiple factors, such as financial or regulatory barriers, logistic challenges, technology-related drivers, users' perceptions, and patient experience (Greenhalgh et al., 2017). The dynamic interaction between these factors might result in the non-adoption or sub-adoption of medical innovations with potentially added benefit (Greenhalgh et al., 2017).

Although the preferred approach to health technology research is based mostly on experimental design, the plain comparison of two alternatives (e.g., in RCTs, or economic evaluations) is not sufficient to understand the whole context (Bauer & Kirchner, 2020). Thus, a more comprehensive approach is needed to map out the factors that might impact the adoption of MR-HIFU in clinical practice. Moreover, to identify what are the most relevant barriers and facilitators and how they interact is necessary to develop an effective implementation strategy (Bauer & Kirchner, 2020).

2. Aim and objectives

The aim of this cumulative dissertation is to generate health economic evidence to inform the adoption of MR-HIFU for the treatment of painful bone metastases in Germany and explore the potential generalizability of findings to the European context. This dissertation comprises three dissertation subprojects previously published in peer-reviewed journals, whose objectives are described below. The research questions and sub-questions guiding the dissertation subprojects are summarized in box 2.

Box 2. Research questions and sub-questions guiding the dissertation subprojects

SUBPROJECT I

- What are the overall costs associated to a standard case of bone metastasis treated with MR-HIFU?
    - What does a care pathway for MR-HIFU look like?
    - What resource consumption should be considered in calculating a hypothetical DRG?

SUBPROJECT II

- What is the value of MR-HIFU for the care of patients with painful bone metastases?
    - What are the clinical and economic consequences of introducing MR-HIFU to the clinical management of patients with bone metastases compared to the current standard of care?
    - What is the value of conducting further research?

SUBPROJECT III

- What are the barriers and facilitators to the adoption of MR-HIFU to the clinical practice of bone metastases in Europe?

2.1. Subproject I

To address the gaps identified in session 1.1 (*Cost and financing of MR-HIFU*), the first subproject aimed (i) to design a care pathway of MR-HIFU for treatment of bone metastases in Europe and (ii) to estimate the resource consumption and the total costs of MR-HIFU service provision for a patient with cancer-induced bone pain from a hospital perspective in Germany.

2.2. Subproject II

The second subproject consisted of an early economic evaluation assessing costs and benefits of MR-HIFU compared to EBRT for pain palliation of bone metastases from the perspective of the German Statutory Health Insurance (SHI). The objectives were (i) to calculate the ICER for the comparison, (ii) to study the sources of uncertainty in the decision and (iii) to determine the value of conducting further research.

2.3. Subproject III

The third subproject had the objective to map the contextual factors influencing the adoption of MR-HIFU, which are not routinely addressed in the RCT design, but could equally impact successful adoption of this technology.

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Chapter III

Methods and key findings of the Dissertation Projects

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1. Summary of subproject I

1.1. Time-driven activity-based costing (TDABC)

The first subproject consisted of a micro-costing study applying the TDABC methodology (da Silva Etges et al., 2019; Keel, Savage, Rafiq, & Mazzocato, 2017). TDABC is a micro costing method developed to allocate resource costs to the final product, by observing the activities within the patient care process (Kaplan & Anderson, 2004). Time is the main measure of resource utilization, what increases the usability for cost accounting. In addition, it enables healthcare providers to observe actual cost savings arising from lean initiatives and process improvements (Kaplan & Porter, 2011).

To calculate the costs associated with the MR-HIFU treatment from the hospital perspective, a stepwise approach was applied (figure 3). Based on interviews with personnel from five centers involved in the FURTHER project, the patient care trajectory was outlined (i.e., steps one and two). Then, cost data and time measurements from the University Hospital of Cologne (UHC) were used to calculate the cost of MR-HIFU for Germany (i.e., steps three to seven). Time measurements were obtained from 18 MR-HIFU bone treatments, including eight prospectively measured in 2020-2021 and ten retrospectively retrieved from technical records from 2018-2019. Time measurements were calculated as mean times (with 5% and 95%-percentiles). Cost data were collected from the controlling department of the UHC, cost components described in four cost categories: personnel, equipment, disposables and overhead (Simões Corrêa Galendi, Yeo, Simic, et al., 2022).

1.2. Key findings: a European care pathway and cost analysis for Germany

The main results of the first project were: a European care pathway and cost allocation framework, and a bottom-up micro costing of MR-HIFU at UHC. The care pathway outlines the care practices of MR-HIFU in five European centers, and contains three levels: macro-, meso-, and micro-level with increasing detail. While the macro level is common to all centers, the micro level provides information on the varying practices. The care pathway should serve as a general

framework for future cost-comparison between centers (Simões Corrêa Galendi, Yeo, Simic, et al., 2022).

The bottom-up micro costing at UHC showed that MR-HIFU costs on average €5,147 for the hospital. At best- and worst-case scenarios the total costs were €4,092 and €5,876, respectively. Additional cost analyses provided a thorough understanding of the hospital costs. For instance, costs with equipment accounted for 41% of total costs (€2,112), followed by costs with personnel (32%, €1,621). Moreover, a trend of reducing costs due to lower MRI occupancy and sonication times was observed when the 2018-2019 cohort was compared to the 2020-2021 cohort (Simões Corrêa Galendi, Yeo, Simic, et al., 2022).

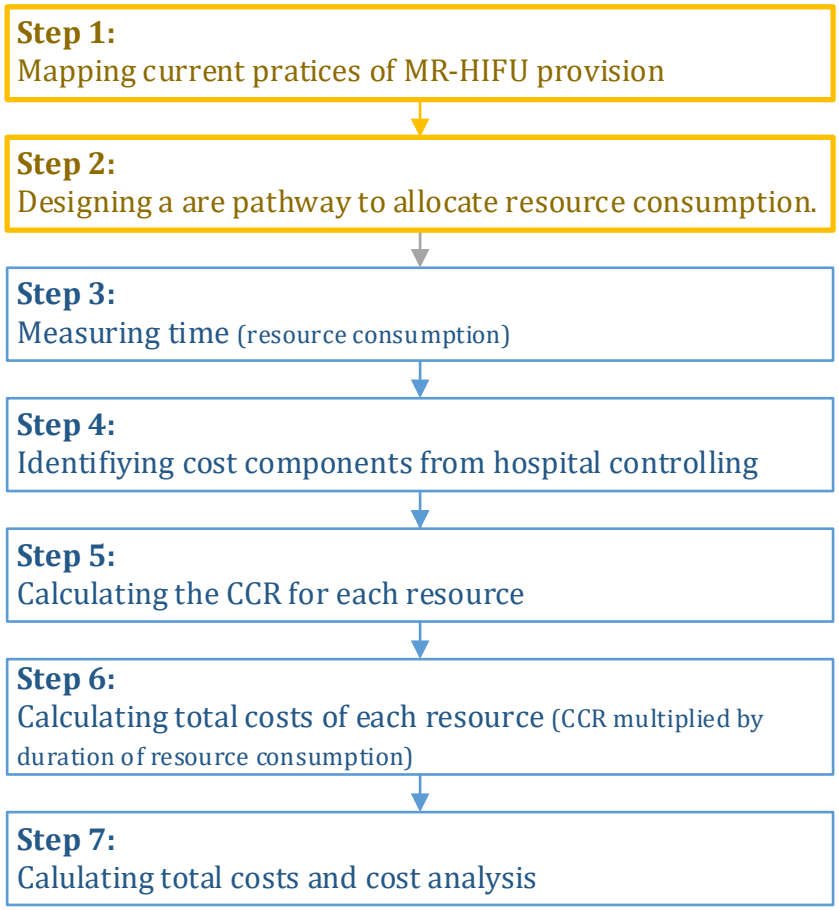

Figure 3. Stepwise approach to the application of time-driven activity-based costing (TDABC) to MR-HIFU. Abbreviations: CCR: capacity Cost Rate (in € /minute), MR-HIFU: Magnetic Resonance Image-guided High-Intensity Focused Ultrasound.

2. Summary of subproject II

2.1. Patient-level simulation modeling

The second subproject consisted of a cost-effectiveness analysis of MR-HIFU compared to EBRT for pain palliation of bone metastases from the perspective of the German SHI. For the main

comparison, two strategies were outlined: MR-HIFU as first-line treatment or retreatment option after failed EBRT (Strategy A) compared to EBRT alone (Strategy B). To reflect the clinical and economic consequences of MR-HIFU and EBRT, a patient-level simulation model was developed using software TreeAge Pro 2019 with a lifetime horizon and a one-month cycle-length.

The choice for a patient-level simulation model instead of a more common cohort model (i.e., Markov model) allowed evaluating dynamic intervention strategies whilst keeping the model structure concise (Siebert et al., 2012). While cohort models (so called Markov models) are memoryless (i.e., they assume that transition probabilities do not depend on patient characteristics or time spent on previous states), patient-level simulation model simulates one patient at a time, as illustrated in figure 4 (Siebert et al., 2012). Thus, patient-level models keep track of each individual's history, what have two main advantages to the current decision problem. First, it enabled the simulation of pathological fractures. Pathological fracture are relevant events that compromise patient quality of life and are costly from a payer perspective. Second, the ease of modeling subgroups according to the primary tumors, which are associated with different life expectancies.

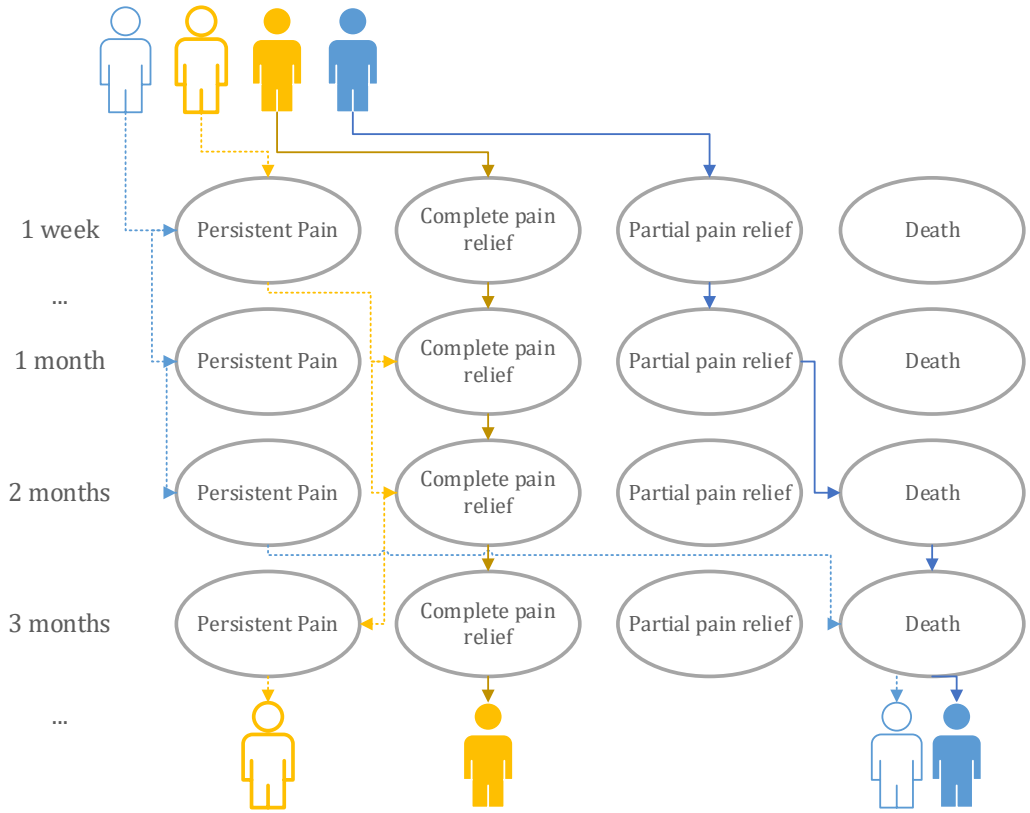

Figure 4. Illustration of how patients move though the patient-level simulation model. Each individual's path throughout the model is trackable. Adapted from Siebert et al., 2012.

To compare the alternatives, the ICER was calculated as cost /pain response (i.e., months spent in complete or partial pain response) and cost /QALY. Subgroup analyses according to primary cancer diagnosis (i.e., breast, prostate, and lung cancer) were performed. Discounting of 3% was applied to costs and benefits according to German guidelines (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2008). An interdisciplinary board of experts validated the model. Deterministic and probabilistic sensitivity analysis were performed. Lastly, a VOI analysis was conducted to estimate the value of collecting additional evidence for reducing the uncertainty of the analysis. Outcomes of the VOI analysis were the expected value of perfect information (EVPI) and the expected value of perfect partial information (EVPPI).

2.2. Key findings: cost-effectiveness of MR-HIFU and VOI analysis

Compared to strategy B (EBRT alone), strategy A (with MR-HIFU) resulted in slightly higher costs (€399) and more benefits (0.02 QALYs and 0.95 months with pain response), with ICERs of €19,845 /QALY and €421 /month with pain response. These results were similar according to cancer subgroups (i.e., breast, prostate, and lung). Moreover, offering MR-HIFU as first-line treatment to all patients at strategy A resulted in higher additional costs (€721 vs. 364 in the base case) and slightly more QALYs (0.023 vs. 0.020 in the base case). The resulting ICER in this scenario (€31,048 /QALY) is 50% higher than the base case (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022).

Results of the probabilistic sensitivity analysis showed that at a WTP of €20,000/QALY, the probability of strategy A being cost effective is 52% (i.e., in 48% of the iterations the additional costs /QALY were above the hypothetical threshold of €20,000). At a WTP of €40,000/QALY, the probability of strategy A being cost effective is 64% and at €60,000/QALY, 69% (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022).

The EVPI for the choice between strategy A and strategy B was €434 /person affected by the decision. Extrapolated to the German population over a period of five years, the EVPI was €178 Mio. These values represent the cost of making the decision based on current (uncertain) evidence and set the maximum amount that should be applied into additional research to reduce uncertainty of the analysis. Additional information on MR-HIFU costs (EVPPI: €329, SD: 5) and the fracture rate following MR-HIFU (EVPPI: €151; SD: 8) would be the most valuable for informing the decision of whether to adopt MR-HIFU (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022).

3. Summary of subproject III

3.1. Group Concept Mapping (GCM)

To investigate the factors influencing the adoption of MR-HIFU in Europe, a GCM study was conducted alongside the FURTHER-trial. Participants were selected through purposive and snowball sampling and included various stakeholders: representatives from medical specialties (e.g., radiologists, radiotherapists, oncologists who refer patients to MR-HIFU), representatives from patients, from technology providers, from regulatory bodies and health technology assessment agencies (Simões Corrêa Galendi et al., 2023).

The study was conducted in two phases (Figure 5). In phase I, participants were asked to brainstorm statements guided by a focus prompt "One factor that may influence the uptake of MR-HIFU in clinical practice in my country is...". In phase II, participants were asked to sort the statements into different piles depending on how they were related to each other; and to rate the statements according to their importance and changeability (Simões Corrêa Galendi et al., 2023).

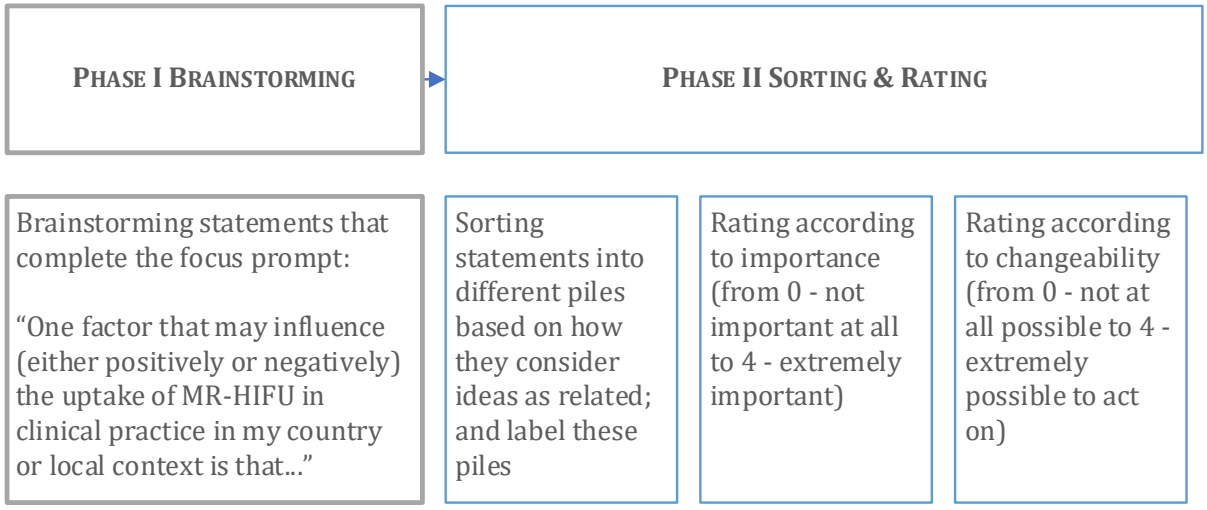

Figure 5. Overview of the group concept mapping study.

To generate a concept map, data generated in the second phase were analyzed through multivariate analyses (i.e., multidimensional scaling and cluster analysis), and the computation of average ratings for each factor and cluster of factors (Simões Corrêa Galendi et al., 2023).

3.2. Key findings: The concept maps

From 79 invited participants, 45 contributed to the brainstorming (n=28) and/or the sorting and rating phase (n=33), resulting in an overall participation rate of 56%. During the first phase, 71 statements were collected. After adjusting for redundancy and potential ambiguity, 49 statements entered phase II.

The resulting concept map comprised 12 clusters of factors: 'competitive treatments', 'physicians' attitudes', 'alignment of resources', 'logistics and workflow', 'technical disadvantages',

'radiotherapy as first-line therapy', 'aggregating knowledge & Improving awareness', 'clinical effectiveness', 'patients' preferences', 'reimbursement', 'cost-effectiveness' and 'hospital costs' (Simões Corrêa Galendi et al., 2023).

Participants sorted statements in a similar manner, but the subgroups per country perceived the importance of these factors slightly differently. In subgroup analysis per country, 'reimbursement' was notably more important in Germany and the Netherlands compared to Italy and Finland. Moreover, cluster 'clinical effectiveness' was perceived as the most important in all countries, except for Italy (Simões Corrêa Galendi et al., 2023).

4. Relation to the FURTHER project

Recruitment for the FURTHER project is still ongoing, thus no clinical data from the main RCT was used in this cumulative dissertation. In subproject I, the European care pathway and cost allocation framework was developed considering practices of five centers from the FURTHER consortium. In subproject III, the FURTHER consortium contributed to participant selection and engagement. Consequently, the findings of this cumulative dissertation are relevant for the European context and several implications to the FURTHER project could be drawn, which will be discussed in *chapter VII*.

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Chapter IV

A time-driven activity-based costing approach of MR-HIFU for cancer-induced bone pain

Journal	International Journal of Hyperthermia

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Statements and Declarations

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- Competing interests: All authors report financial support of the European Union's Horizon 2020 programme for the submitted work (Grant No 825859). Dr. Sin Yuin Yeo has a part time position with Profound Medical GmbH, outside of the submitted work.
- Informed consent: Written informed consent was not required for this study because no individual patient data was collected.
- Ethical approval: Institutional Review Board approval was not required because no individual patient data was collected.

Abstract

Objective: To determine resource consumption and total costs for providing Magnetic Resonance-guided High-Intensity Focused Ultrasound (MR-HIFU) treatment to a patient with cancer-induced bone pain (CIBP).

Methods: We conducted a time-driven activity-based costing (TDABC) of MR-HIFU treatments for CIBP from a hospital perspective. A European care-pathway (including a macro-, meso- and micro-level) was designed to incorporate the care-delivery value chain. Time estimates were obtained from medical records and from prospective direct observations. To calculate the capacity cost rate, data from the controlling department of a German university hospital were allocated to the modules of the care pathway. Best- and worst-case scenarios were calculated by applying lower and upper bounds of time measurements.

Results: The macro-level care pathway consisted of eight modules (i.e., outpatient consultations, pre-treatment imaging, preparation, optimization, sonication, post-treatment, recovery, and anesthesia). The total cost of an MR-HIFU treatment amounted to €5,147 /patient. Best- and worst-case scenarios yielded a total cost of €4,092 and to €5,876. According to cost categories, costs due to equipment accounted for 41% of total costs, followed by costs with personnel (32%), overhead (16%) and materials (11%).

Conclusion: MR-HIFU is an emerging non-invasive treatment for alleviating CIBP, with increasing evidence on treatment efficacy. This costing study can support MR-HIFU reimbursement negotiations and facilitate the adoption of MR-HIFU as first-line treatment for CIBP. The present TDABC model creates the opportunity of benchmarking the provision of MR-HIFU to bone tumor.

Keywords: High-Intensity Focused Ultrasound Ablation, Magnetic Resonance Imaging Interventional, Cancer Pain, Cost and Cost Analysis, Hospital Costs

1. Introduction

Cancer-induced bone pain (CIBP) is a condition associated with bone metastases or other musculoskeletal tumors that affects the quality of life and the functionality of patients (Lipton, 2010; Portenoy, 2011; Ripamonti & Fulfaro, 2001). For patients with persistent CIBP despite the use of opioids, palliative loco regional external beam radiotherapy (EBRT) is the treatment of choice (Chow et al., 2014; Huisman et al., 2015; Ripamonti & Fulfaro, 2001). Although approximately 60-70% of patients respond to radiotherapy, it takes on average four weeks for EBRT to achieve adequate pain relief (Jones, Lutz, Chow, & Johnstone, 2014; van der Linden et al., 2004; Westhoff et al., 2015). Because immediate and efficient pain relief is the main treatment goal, particularly in the palliative setting, patients may benefit from treatment alternatives offering a faster pain palliation.

Magnetic Resonance-guided High-Intensity Focused Ultrasound (MR-HIFU) is an emerging non-invasive treatment modality that can be performed either as alternative or in addition to EBRT (Bartels et al., 2021; Lee et al., 2017). HIFU delivers targeted acoustic energy to increase temperature (T > 56 °C) at the intended treatment region to thermally ablate the periosteal nerve and tumor. HIFU can be performed under the guidance of magnetic resonance imaging (MRI), which provides excellent soft tissue contrast images for treatment planning. During treatment, MRI thermometry provides a near real-time assessment of temperature and thermal-dose distribution on soft tissues. This enables monitoring the thermal damage on the treated and surrounding healthy tissues, and modulation of the energy level in case the temperature rise is insufficient (Scipione et al., 2018).

MR-HIFU has shown promising results for the management of CIBP, caused by bone metastasis or other musculoskeletal tumors (Scipione et al., 2018; Siedek et al., 2019). Evidence on the safety and effectiveness of MR-HIFU as a first line modality for pain palliation in skeletal metastases was demonstrated in an early prospective cohort, in which complete pain control was achieved in 13 of the 18 treated patients (72.2%) (Napoli, 2013). In addition, a randomized placebo-controlled trial including 147 patients demonstrated effectiveness of MR-HIFU in alleviating pain within few days after treatment in about two-thirds of patients. In this trial, 47% of patients reduced or stopped opioid consumption (Hurwitz et al., 2014). The beforementioned emerging evidence on safety and effectiveness provides strong impetus for further uptake in clinical practice. However, the costs and cost-effectiveness of MR-HIFU for CIBP are still uncertain.

European countries increasingly move towards payments based on diagnosis-related-groups (DRG) (e.g., Germany, the Netherlands, Finland) (Tan, 2014). To promote the integration of innovative medical devices such as MR-HIFU into the DRG scheme, hospitals have to collect cost-accounting data, to adjust and update the DRG-tariffs, and therefore allow fair

reimbursement (Allin et al., 2019). Additionally, an exact cost calculation is the precondition for health-economic analyses aiming at comparing health outcomes and costs (Huisman et al., 2015). Defining resource consumption and the resulting costs is one of the critical first steps for adopting MR-HIFU into the treatment of painful bone lesions.

The objective of the present micro costing study was to estimate resource consumption and the total costs of MR-HIFU service provision for a patient with cancer-induced bone pain from a hospital perspective.

2. Materials and Methods

To calculate the costs associated with the MR-HIFU treatment from a hospital perspective, this micro-costing study followed a stepwise approach to the application of Time Driven Activity-Based Costing (TDABC) in health-care settings (da Silva Etges et al., 2019; Keel, Savage, Rafiq, & Mazzocato, 2017). TDABC is a micro costing method developed to allocate resource costs to products through observing the activities performed in the production process (Kaplan & Anderson, 2004). TDABC uses time as the unique driver of resource utilization which allows efficient and precise cost estimations. In addition, it enables healthcare providers to capture actual cost savings from lean initiatives and process improvements (Kaplan & Porter, 2011).

The following seven steps were undertaken. First, process maps outlining the patient care trajectory were developed. Second, a care pathway was designed to allocate all relevant resources consumption, thus reflecting the care delivery value-chain. Third, time measurements were performed. Fourth, the cost of each resource component was summed up. Fifth, the capacity cost rate (CCR) of each resource component was calculated, considering its annual availability. Sixth, we calculated the total costs of each resource by multiplying the CCRs and duration of resource consumption. Finally, the total cost of a MR-HIFU treatment for CIBP was calculated and allocated according to the modules of the care pathway.

In view of subsequent implementation in a European multi-centric clinical trial setting (Clinical.trials.gov registration number NCT04307914), we aimed at building a cost allocation framework that would be applicable across different European centers (i.e., steps one and two). Then, to demonstrate the potential of the cost allocation framework, we conducted a micro costing study by applying data on costs and time measurements from the University Hospital of Cologne (UHC), Germany (i.e., steps three to seven).

2.1. Development of the care pathway

With the objective to map out the current practices of MR-HIFU in five European centers, personnel responsible for delivering MR-HIFU treatments in each center were asked to describe

their activities from the referral to MR-HIFU treatment until discharge from the hospital. Description of the participants is available on table 1A (ESM). Process maps were created using Microsoft Visio and submitted to the personnel iteratively, until no new activity was added. Macro-, meso- and micro-level care pathways were developed, containing all activities performed during the provision of MR-HIFU at an increasing level of details.

2.2. Measurement of resource consumption

Resource consumption was based on observations at the UHC. Because the units of observation were the processes that compose patient care, no individual patient data were collected. The personnel responsible for delivering MR-HIFU treatments at UHC provided estimations of time spent on each activity of the process map and probability that each activity takes place. Additionally, time measurements were collected both prospectively and retrospectively.

Duration of activities and resource consumption were prospectively measured for eight consecutive MR-HIFU bone treatments performed from June 2020 to May 2021. Retrospective time estimates were retrieved from technical records of ten consecutive cases treated from 2018 to 2019. From these records, information about logistics (i.e., MRI room occupancy, usage of gel pad) and treatment duration (i.e., technical report generated by the HIFU equipment) was obtained. Duration of resource consumption for all modules and activities were provided as mean times (with 5% and 95%-percentiles), calculated using SPSS (IBM Corp. IBM SPSS Statistics for Macintosh, Version 27.0. Armonk, NY). Table 1 summarizes all probabilities and time variables. A comparative analysis of the prospective and retrospective case series is shown in figures 1-2A in the ESM.

For the base case, the total costs of MR-HIFU were calculated based on prospectively measured mean time estimates preferably. In case these were not available, we applied retrospectively collected data or estimations from experts, in that order. Best- and worst-case scenarios were calculated by applying the lower and upper bounds of time measurements (i.e., 5% and 95%-percentiles).

Table 1. Treatment times and probabilities (estimations from treatment providers, prospective and retrospective data from a German hospital).

Module of the care pathway (Macro level)	Activity meso-level	Probability of resource consumption[a]	Estimation from personnel in minutes[a]	Time measurements (in minutes)	
				Prospective[b]	Retrospective[b]
Outpatient consultation	Interventional Radiologist assessment	1	60	-	-

Pre-treatment imaging	Pre-treatment MRI	0.8	45	-	-
	Pre-treatment CT	0	20	-	-
Preparation	Preparation of the MRI room	1	45	110 (91-129)	181 (121-241)
	Time spent interventional Radiologist	1	30	107 (73-141)	
Optimization	Positioning	1	150	103 (78-128)	79.9 (40-114)
	Test sonication	1	2	3.9 (2.9 – 4.6)	
Sonication	Sonications	1	105	89 (57 – 120)	93 (58-128)
Post-treatment	Post-treatment imaging (MRI)	1	20	45 (21- 69)	47 (31-63)
	Cleaning of MRI room	1	15		
Recovery	Stay at the recovery room	1	180	202 (139 – 265)	179 (151-207)
	Overnight at clinical ward	1	720-960	886 (843- 928)	922 (865–979)
Anesthesia	General anesthesia (from arrival of Anesthesia team to extubating)	1	335	314 (257- 370)	-

a. estimations from personnel from the University Hospital of Cologne; b. mean time measurements (5 and 95 percentiles). Abbreviations. MRI: Magnetic Resonance Imaging, CT: Computerized Tomography.

2.3. *Valuation of resource consumption*

Data on prices were collected from the controlling department of the UHC, cost components separated into cost categories (i.e., personnel, equipment, disposables and overhead). Personnel costs included gross salary, capital-forming benefits, and social contributions. Overhead costs (i.e., the costs of energy, housing, maintenance, and administration) were calculated considering the facility size in square meters and the average capacity of the departments. Costs of housing and administration were approximated according to the hospital accounting practices (€17.65 /day), while energy costs were calculated per square meters (m^2) of net floor space (Blum, Löffert, Offermanns, & Steffen, 2014).

Equipment costs referred to the replacement costs obtained from the providers, adjusted for the lifespan of the equipment, and expected depreciation; expenses with maintenance were also considered.

Based on the capacity (availability) and full cost of each resource component, we calculated the respective capacity cost rate (CCR) in €/min. Cost input parameters are described in table 2. For personnel, available capacity was estimated by subtracting vacations, holidays, breaks and weekends as per institutional policies from the full calendar year. For equipment, the operational capacity was the expected capacity of a given resource to operate. The current operational hours HIFU equipment is 10 hours/day, 1 day/ week (MRI equipment: 10 hours/day, 250 days/year). In addition, we calculated an alternative scenario where the HIFU operational capacity was doubled (i.e., 2 days a week).

Costs of anesthesia were derived from a previous study that calculated case-related revenues per minute for specific DRGs in a German hospital (Waeschle et al., 2016). All costs were adjusted for the target year of 2021.

Table 1. Capacity cost rates (€/min)

Cost category	**Capacity Cost Rate (CCR)**
Personnel	
Interventional Radiologist	€1.54 /min
Technician	€0.64 /min
Anesthesiologist	€1.25 /min
Anesthesiologist assistant	€0.61 /min
Equipment	
MRI Ingenia 3T[a]	€3.72 /min
HIFU Profound (Sonalleve)[a]	€5.11 /min
Materials	
Gel pad 40mm	€325 /unit
Gel pad 15mm	€152 /unit
Degassed water	€10
Anesthesia [a]	€119
Intravenous contrast media (Gadoteric acid 15 ml)	€109
Overhead[c]	
MRI room	€1.53 /min
Outpatient consultation	€0.25 /min
Recovery room	€0.28 /min
Clinical ward	€0.19 /min

All costs obtained from the controlling department of the University Hospital of Cologne, exception for: [a] replacement cost obtained from providers and [b]estimated based on literature. (Waeschle et al., 2016)

[c] Considering energy, housing, maintenance, and administration. Abbreviations: MRI: Magnetic resonance imaging; HIFU: High-Intensity Focused Ultrasound

3. Results

3.1. European care pathway and cost allocation framework

Figure 6 shows the macro-, meso- and micro-level care pathways that accounted for all activities performed during patient care at increasing level of detail. Entry point to the care pathway was determined by the referral to the MR-HIFU treatment. Exit point was the patient's discharge from hospital after full recovery from the procedure. Follow up consultations are performed in outpatient setting by the assisting physician (e.g., clinical oncologist or orthopedic oncologist) and were not considered.

The macro-level consisted of eight modules (i.e., outpatient consultations, pre-treatment imaging, preparation, optimization, sonication, post-treatment, recovery, and anesthesia). Outpatient consultation referred to the appointment with the interventional radiologist for medical assessment and informed consent. Pre-treatment imaging consist of any imaging needed before treatment day, and may involve MRI or computerized tomography, according to the case requirements and depending on the availability of images from the ongoing oncologic follow up.

The MR-HIFU treatment was separated in three modules: (i) the preparation module contains all activities for preparing the patient and the MRI room (e.g., dressing for treatment, quality assurance test); (ii) the optimization module starts with positioning the patient at the HIFU table, includes the planning MRI, and finishes with the test sonication; (iii) the sonication module refers to the therapeutic sonications and respective cooling time.

The post-treatment module includes one control MRI and cleaning the MRI room. Lastly, the recovery module includes a stay at the recovery room, overnight at the clinical ward and the assessment of meanwhile occurred adverse events by a medical professional before discharge. We considered 'anesthesia' as a quasi-detached module.

The choice of the anesthesia is at the discretion of the anesthesiologist on duty, and the practices varies among the five centers studied (table 2A, ESM). As per institutional practices at the UHC, all patients undergoing MR-HIFU treatment undergo general anesthesia.

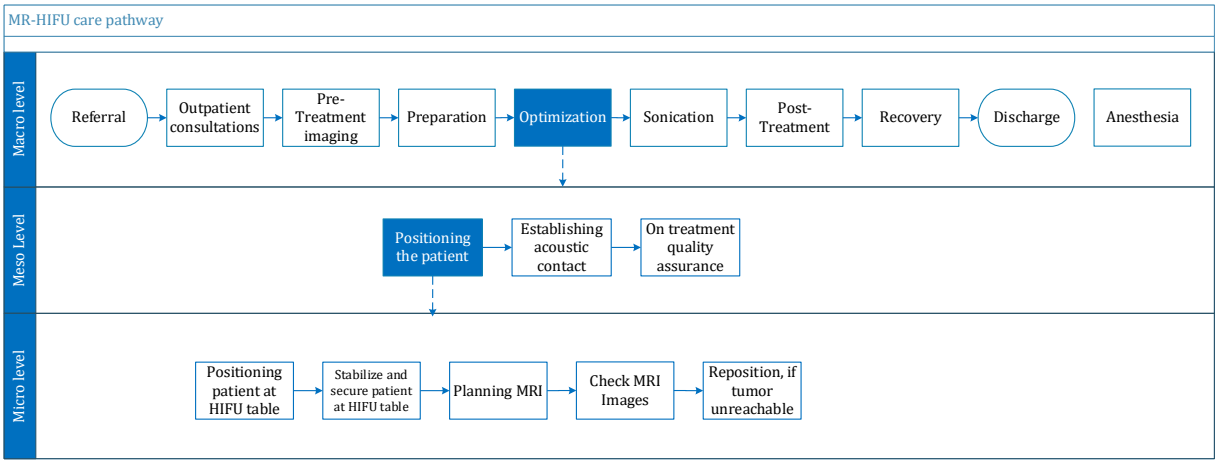

Figure 6. Care pathway for MR-HIFU treatment.

3.2. Micro costing of MR-HIFU

In the base case, the total costs per patient with cancer-induced bone pain treated with MR-HIFU were €5,147. Figure 7 shows the costs per patient per module of the care pathway. Costs of outpatient consultations (mainly personnel costs) accounted for only 2% of total costs. The modules that yielded the higher costs were: preparation module accounted for 11% of costs, optimization for 26% and sonication for 23%. Costs allocated to anesthesia (i.e., personnel, overhead and disposables) represented 17% of the total costs.

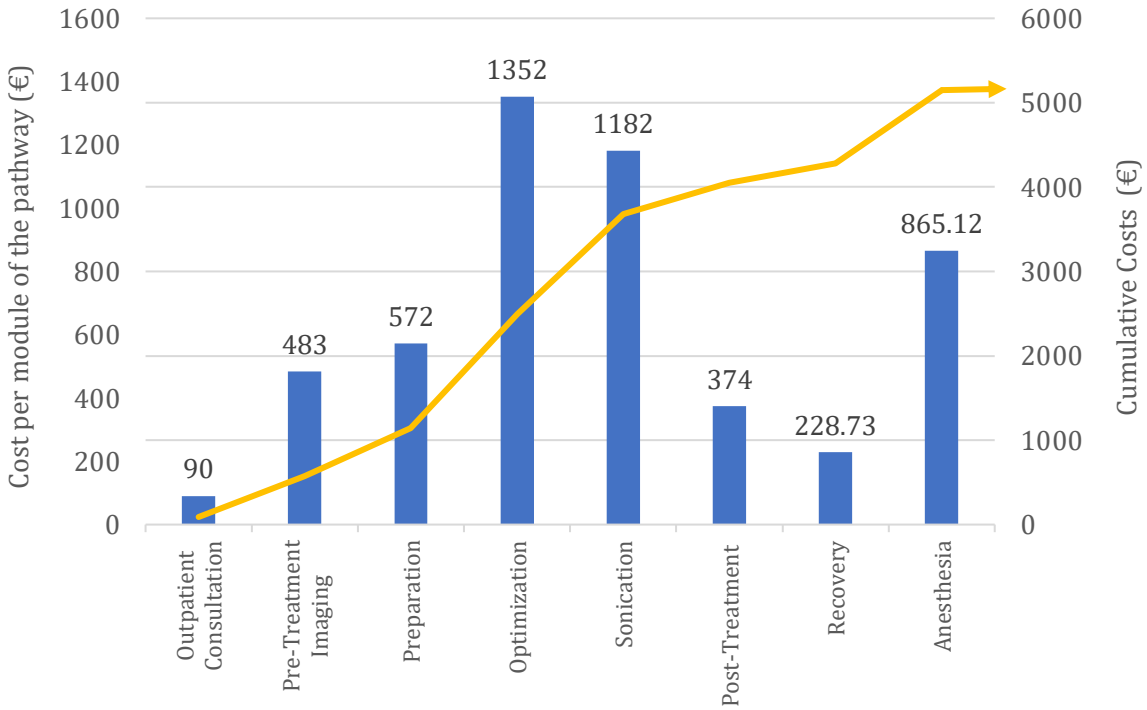

Figure 7. Costs (€) per patient per module of the care pathway (macro-level). The line represents cumulative costs as the care pathway progresses.

According to cost categories, costs in the base case with equipment accounted for 41% of total costs (€2,112), followed by costs with personnel (32%, €1,621), Overhead (16%, €842) and materials (11%, €572). Medical personnel (i.e., interventional radiologist and the anesthesiologist) represented 56% of personnel costs. Figure 8 shows how costs were distributed in each module of the care pathway, according to cost categories.

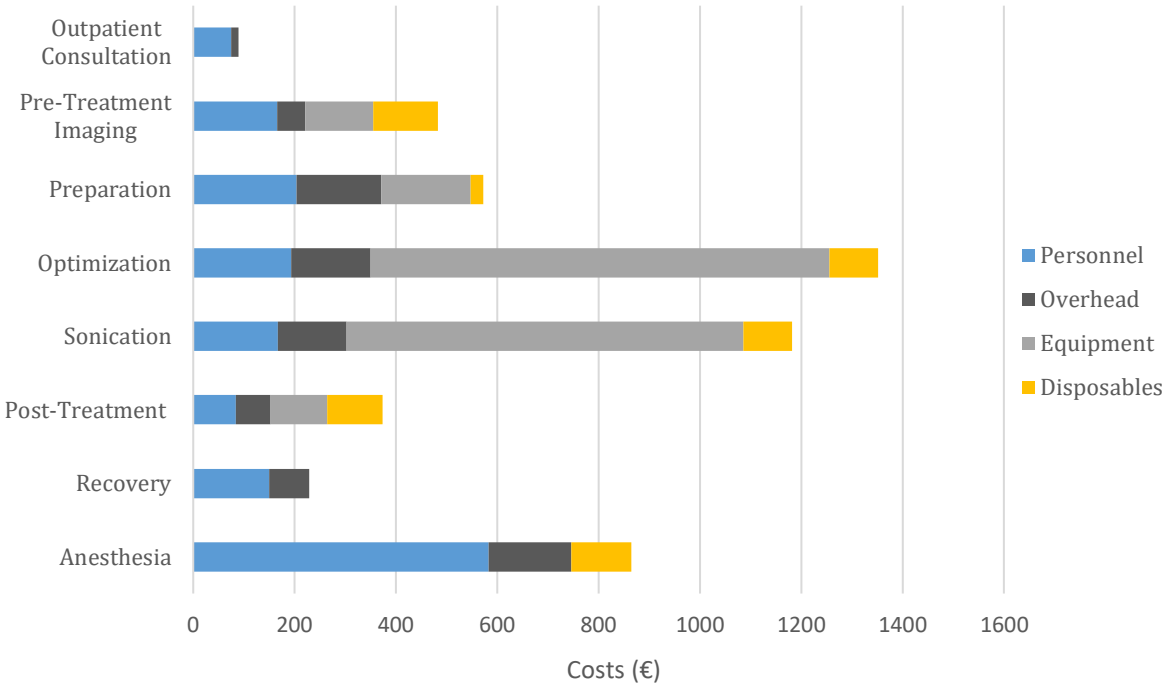

Figure 8. Costs (€) allocated according to cost categories in each module of the care pathway (macro-level).

Best- and worst-case scenarios yielded total costs of €4,092 and €5,876, respectively. If the operational hours of HIFU were increased to 2 days/week, without changing CCR of the MRI equipment, the total costs per patient would reduce from €5,147 to €4,443. Assuming this increased capacity of HIFU equipment, (i.e., CCR of the HIFU equipment of €2.55 /min) would impact the most costly modules of the care pathway, saving €262 on optimization module and €227 on sonication module (Figure 3A in the ESM).

4. Discussion

There is growing evidence on the effectiveness of MR-HIFU treatment for patients with CIBP (Hurwitz et al., 2014; Napoli, 2013). To support the adoption of MR-HIFU in the clinical practice, an early evaluation of the technology from a health economic perspective was needed. By applying a TDABC approach, our results show that the hospital costs for the provision of MR-

HIFU for patients with bone tumors at the UHC currently amounts to €5,146 /patient (i.e., €4,092 and €5,876 on best- and worst-case scenarios).

In Germany, the G-DRG system and its standardized cost-accounting scheme are used for both national reimbursement and strategic management decisions in hospitals (Vogl, 2012). To calculate costs at different aggregation levels (e.g. department, DRG group, case), the traditional cost accounting scheme dictated by the German Institute for the Hospital Remuneration System (InEK) relies on cost categories and cost centers (Vogl, 2012).

There were two differences to the traditional cost accounting scheme in our analysis. First, the cost categories were anchored to a care pathway, what results in more transparency on resource utilization. (Feyrer, Rösch, Weyand, & Kunzmann, 2005) Second, capital costs are not usually included in the G-DRG calculation, because German hospitals are funded according to the dual financing scheme; while statutory health insurance incur operating costs, capital costs are financed by the German states or federal grants through tax revenues (Tan, 2014). However, capital costs are relevant for the hospital, and its consideration in the G-DRG calculation could lead to more efficient capital asset utilization, transparent and efficient cost- and activity control (Vogl, 2014).

In German hospitals, reimbursement via DRG-based payments account for 80% of hospital costs. (Tan, 2014) However, the time-lag until an innovative technology is integrated in the DRG scheme may take up to three years (Ex, Vogt, Busse, & Henschke, 2020). To promote faster adoption of potentially beneficial innovative medical devices, German hospitals can negotiate for additional funding (i.e., innovation payments). In order to receive an innovation payment the hospital is required to prove that the current DRG-tariff does not cover the costs for the procedure (Ex et al., 2020). Although this early assessment of costs associated with MR-HIFU treatment should not be used to set reimbursement policy, it may serve as a guide for hospitals to inform reimbursement negotiations.

While the costs of adverse events should be taken into account in costing studies of medical procedures, in our analysis no resource consumption related to adverse events were observed, presumably because adverse events related to MR-HIFU are rare. In a phase III trial, the most clinically significant adverse event, and possibly the one associated with higher costs, was a third-degree skin burn, observed in one out of 112 patients due to noncompliance with treatment guidelines (Hurwitz et al., 2014). However, the developed care pathway would capture the main costs associated with adverse events, given that most adverse events are transient and resolved on treatment day (Hurwitz et al., 2014).

The operational capacity of the HIFU equipment applied in our base case (i.e., one day /week) reflects the early implementation phase of this technology. As the technology is further implemented into clinical practice, a trend to cost reduction can be assumed. In a scenario

analysis, and the cost per patient treated with MR-HIFU dropped €540 when an increased operational capacity was considered; particularly because it leads to better capital asset utilization. Besides, cost reduction may result from incremental innovation of the MR-HIFU technology (e.g., reducing treatment duration, or dismissing the need for pre-treatment or control imaging). However, the dynamic nature of innovation is particularly challenging to capture in economic evaluations of medical devices (Drummond, Griffin, & Tarricone, 2009).

Moreover, because MR-HIFU is still on early phase of implementation, an overestimation of costs may exist due to the learning curve. Whilst the treatment providers gain in experience, selection of the most optimal cases for HIFU treatment from the positioning perspective (i.e., target lesions that are easier to reach and smaller tumors) can reduce treatment duration and costs. Although the impact of a learning curve on clinical outcomes is assessed regularly, little is known of its impact on costs (Drummond et al., 2009).Previous assessments of the learning curve for HIFU treatment of fibroids show that satisfactory performance is stable after 11 procedures (Chen et al., 2018), and treatment duration become stable at the 16th case (Park, Kim, Keserci, Rhim, & Lim, 2013). With respect to the time measurements collected at the UHC, a comparative analysis of the cohort of patients treated from 2018-2019 versus 2020-2021 shows a trend of reducing MRI occupancy and sonication times. This circumstantial evidence might reflect the learning curve and gain of experience. However, the difference in methods for time measurements (i.e., retrospective versus prospective) does not allow to draw firm conclusions.

Attempts to allocate healthcare costs to processes such as Activity-Based Costing (ABC) have shown to be challenging and resource consuming (Kaplan & Porter, 2011). Hence, the TDABC method was proposed as an evolution of the ABC method that still accommodates the complexity inherent to healthcare organizations to the patient level, but uses time as main cost-driver (Kaplan & Anderson, 2004). In recent years, TDABC has most often been used to calculate costs of inpatient procedures, to identify improvement opportunities in the workflow, or to support value-based initiatives (Etges, Ruschel, Polanczyk, & Urman, 2020). In addition, TDABC enables healthcare providers to direct the attention of clinicians and managers to expensive and inefficient processes (Kaplan & Witkowski, 2014).

The TDABC approach creates the opportunity of benchmarking the provision of MR-HIFU to bone tumors. Benchmarking can not only support the identification of cost-saving initiatives but also improve the quality of care (da Silva Etges et al., 2019; Feyrer et al., 2005). Because the developed pathway reflects care practices from several European centers, it should be applicable to other centers and allow cost comparisons. It is noteworthy that the care pathway loses generalizability from macro- to the micro-level, whereas it gains in specificity for the care practices of the centers studied.

Among the centers that contributed to the development of the care pathway, the choice of the anesthesia technique varied the most, with potential impact on costs. While at the UHC all patients undergo a general anesthesia, spinal anesthesia with conscious sedation is preferred in other countries. In open surgeries, spinal anesthesia has shown to be cost saving when compared to general anesthesia, due to faster recovery and less blood loss (Agarwal, Pierce, & Welch, 2016; French, Guzman, Rubio, Frenzel, & Feeley, 2016). However, for the purpose of MR-HIFU general anesthesia may facilitate positioning and reduce motion during treatment (Yao, Trinh, Wong, & Irwin, 2008), which could reduce the duration of the procedure, thereby reducing costs. Therefore, centers that prefer spinal anesthesia for radiologic procedures should pursue measuring time locally, instead of transposing the input parameters from the UHC.

A previous cost-effectiveness modelling study from the U.S. showed that MR-HIFU for patients with CIBP results in both additional costs and quality-adjusted life years (QALY), yielding an incremental cost-effectiveness ratio of $54,160 /QALY (Bucknor, Chan, Matuoka, Curl, & Kahn, 2020). In that study, the costs of MR-HIFU applied to the model considered micro costing from two institutions and reimbursement data from Medicare and varied widely from $ 5,680 to $20,000. Moreover, the uncertainty around the real costs of MR-HIFU affected the result (e.g., the incremental cost-effectiveness ratio dropped 25% if the MR-HIFU costs were $10,000 instead of $15,000) (Bucknor et al., 2020). Hence, a precise cost calculation of MR-HIFU may improve the validity of future cost-effectiveness analysis that aim to compare MR-HIFU with other treatment alternatives such as radiotherapy.

Some limitations to our time input parameters must be acknowledged. First, for some activities of the care pathway (i.e., outpatient consultations), we relied on estimations from personnel, which are less precise due to potential recollection bias. However, the impact on total costs is probably negligible because the cost variables associated to these activities were the lowest. Second, we did not evaluate if clinical variables and patient characteristics can predict longer treatment duration and higher costs. The impact of clinical variables, such as tumor volume or target lesion size, on costs will be assessed by applying this TDABC approach in a European multicentric clinical trial setting (NCT04307914), in which treatment duration will be prospectively measured for patients with bone metastasis.

Third, in our analysis the time measurements were performed for all types of bone tumors, including bone metastasis, desmoid tumors and osteoid osteomas. Unfortunately, the small sample size did not allow to observe trends for resource use in different subgroups. To solve the remaining uncertainties regarding learning curve and cost trends per tumor subgroup a larger number of observations and time measurements is needed.

5. Conclusion

In conclusion, the adoption of MR-HIFU as a first-line treatment alternative for the treatment of CIBP will follow the growing evidence on its clinical effectiveness. This TDABC approach provides a reproducible tool for cost-accounting of MR-HIFU and an early assessment of costs incurred by the provision of MR-HIFU for patients with bone tumors at the UHC, what will play an important role in driving adoption from a health economic perspective.

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Chapter V

Early economic modeling of MR-HIFU compared to radiotherapy for pain palliation of bone metastases

Journal	Frontiers in Oncology

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Statements and Declarations

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Abstract

Introduction: Magnetic Resonance Image-guided High-Intensity Focused Ultrasound (MR-HIFU) is a non-invasive treatment option for palliative patients with painful bone metastases. Early evidence suggests that MR-HIFU is associated with similar overall treatment response, but more rapid pain palliation compared to external beam radiotherapy (EBRT). This modelling study aimed to assess the cost-effectiveness of MR-HIFU as an alternative treatment option for painful bone metastases from the perspective of the German Statutory Health Insurance (SHI).

Materials and Methods: A microsimulation model with lifelong time horizon and one-month cycle length was developed. To calculate the incremental cost-effectiveness ratio (ICER), strategy A (MR-HIFU as first-line treatment or as retreatment option in case of persistent pain or only partial pain relief after EBRT) was compared to strategy B (EBRT alone) for patients with bone metastases due to breast, prostate, or lung cancer. Input parameters used for the model were extracted from the literature. Results were expressed as € /quality-adjusted life years (QALYs) and € /pain response (i.e., months spent with complete or partial pain response). Deterministic and probabilistic sensitivity analyses (PSA) were performed to test the robustness of results, and a value of information analysis was conducted.

Results: Compared to strategy B, strategy A resulted in additional costs (€399) and benefits (0.02 QALYs and 0.95 months with pain response). In the base case, the resulting ICERs (strategy A vs. strategy B) are €19,845 /QALY and €421 /pain response. Offering all patients MR-HIFU as first-line treatment would increase the ICER by 50% (€31,048 /QALY). PSA showed that at a (hypothetical) willingness to pay of €20,000 /QALY, the probability of MR-HIFU being cost effective was 52%. The expected value of perfect information (EVPI) for the benefit population in Germany is approximately €190 Mio.

Conclusion: Although there is considerable uncertainty, the results demonstrate that introducing MR-HIFU as a treatment alternative for painful bone metastases might be cost effective for the German SHI. The high EVPI indicate that further studies to reduce uncertainty would be worthwhile.

Keywords: Bone metastases, pain palliation, cancer pain, cost-effectiveness, high-intensity focused ultrasound, MR-HIFU, radiotherapy

1. Introduction

Bone metastases occur in 65% of patients with advanced solid cancer, particularly originating from malignancies of the lung, prostate, and breast. For these patients, pain is a common and devastating symptom affecting both quality of life and functionality (Lipton, 2010; Portenoy, 2011; Ripamonti & Fulfaro, 2001). Opioids are regularly the baseline pharmacologic treatment for pain palliation. However, high doses required to manage pain effectively are associated with numerous adverse effects (Portenoy, 2011). Since patients with persistent pain often require additional focal treatment, loco regional external beam radiotherapy (EBRT) is the current standard of care for patients with bone metastases (Chow et al., 2014; Huisman et al., 2015; Ripamonti & Fulfaro, 2001).

Approximately 60-70% of patients initially respond to EBRT over the course of four weeks following treatment (Jones, Lutz, Chow, & Johnstone, 2014; van der Linden et al., 2004; Westhoff et al., 2015). However, among those adequately responding to EBRT, about 50% experience recurrent pain (Huisman et al., 2012). For those non-responding to EBRT or suffering recurrent bone pain, re-irradiation is limited as cumulative radiation doses might be harmful for organs at risk surrounding the target lesion. In addition, only 58% of patients undergoing re-irradiation benefit from it (Huisman et al., 2012).

Magnetic Resonance Image-guided High-Intensity Focused Ultrasound (MR-HIFU) is a non-invasive treatment modality that may substantially improve pain palliation and can be offered as first-line treatment or after prior radiation (Huisman et al., 2015). A randomized placebo-controlled trial demonstrated that MR-HIFU is superior to placebo after 3 months: the response rate for the primary endpoint (improvement in self-reported pain) was 64% in the MR-HIFU arm compared to 20% in the placebo arm ($P < .001$) (Hurwitz et al., 2014). Although to date there is no randomized controlled trial (RCT) comparing MR-HIFU with EBRT directly, a single-center matched-pair study showed similar overall treatment response rates but faster pain relief using MR-HIFU compared to EBRT (pain relief in 71% vs. 26% at 1 week, $p = 0.0009$ and 81% vs. 67%, $p = 0.3753$ at 1 month) (Lee et al., 2017). Moreover, MR-HIFU has less side effects (Huisman et al., 2015).

An early assessment of the cost-effectiveness of adding MR-HIFU as first-line treatment or after prior radiation compared to EBRT can provide an appraisal of the potential value of this new technology (e.g., to support reimbursement decisions, investment in installation of medical infrastructure and research prioritization). This economic modelling study assessed the cost-effectiveness of MR-HIFU as treatment alternative for the palliative treatment of patients with

bone metastases in comparison to the current standard of care (i.e., EBRT alone), from the perspective of the Statutory Health Insurance (SHI) in Germany.

2. Materials and Methods

To reflect the clinical and economic consequences of MR-HIFU and EBRT for the treatment of bone metastases, we developed a patient-level simulation model (software TreeAge Pro 2019) with a lifetime horizon and a one-month cycle length. The cycle length was chosen because retreatment of patients with painful bone metastases can be considered after one month of persistent pain (Lutz et al., 2017). The analysis was performed from the perspective of the SHI which covers 87% of the German population (Busse, Blümel, Knieps, & Bärnighausen, 2017).

Patients entering the model were assumed to be male and female adults with non-vertebral painful bone metastases originating from lung cancer, prostate cancer, or breast cancer in an even distribution. The model population reflected that over 80% of bone metastases from solid tumors arise from cancers of the breast, prostate, or lung (Svensson, Christiansen, Ulrichsen, Rørth, & Sørensen, 2017). In the model, patients were referred to treatment with MR-HIFU or EBRT due to significant pain (scoring at least four by the Numerical Rating Scale, NRS), having received optimal pain management with opioids.

2.1. Strategies for the comparison

For the main comparison, two strategies were outlined. Strategy A was defined as MR-HIFU either as a first-line treatment (about 60%) or as retreatment option after failed EBRT (about 40%). In strategy A, not all patients received MR-HIFU as first line-treatment because in a realistic scenario MR-HIFU is unlikely to replace EBRT completely as first-line treatment. Patients who receive EBRT as a first-line treatment were assumed to be re-treated with MR-HIFU in case of persistent pain or only partial pain relief. The proportions were chosen to confer more internal consistency with the trial informing data on MR-HIFU effectiveness (Hurwitz et al., 2014). Strategy B reflected the standard of care practice in Germany, defined as EBRT followed by re-irradiation in case of persistent pain. The EBRT dose was mainly multi-fraction (i.e., 20Gy in five daily fractions), and single-fraction (eight Gy in one fraction) for 10% of cases, reflecting the preferred practices in German radiotherapy institutions (Adamietz, Schneider, & Müller, 2002; Lievens, Kesteloot, Rijnders, Kutcher, & Van den Bogaert, 2000), and recommendations for treatment of patients with more favorable prognosis (i.e., life expectancy more than four weeks) from the German guideline (Leitlinienprogramm Onkologie, 2017). Figure 9 shows the strategies for the comparison.

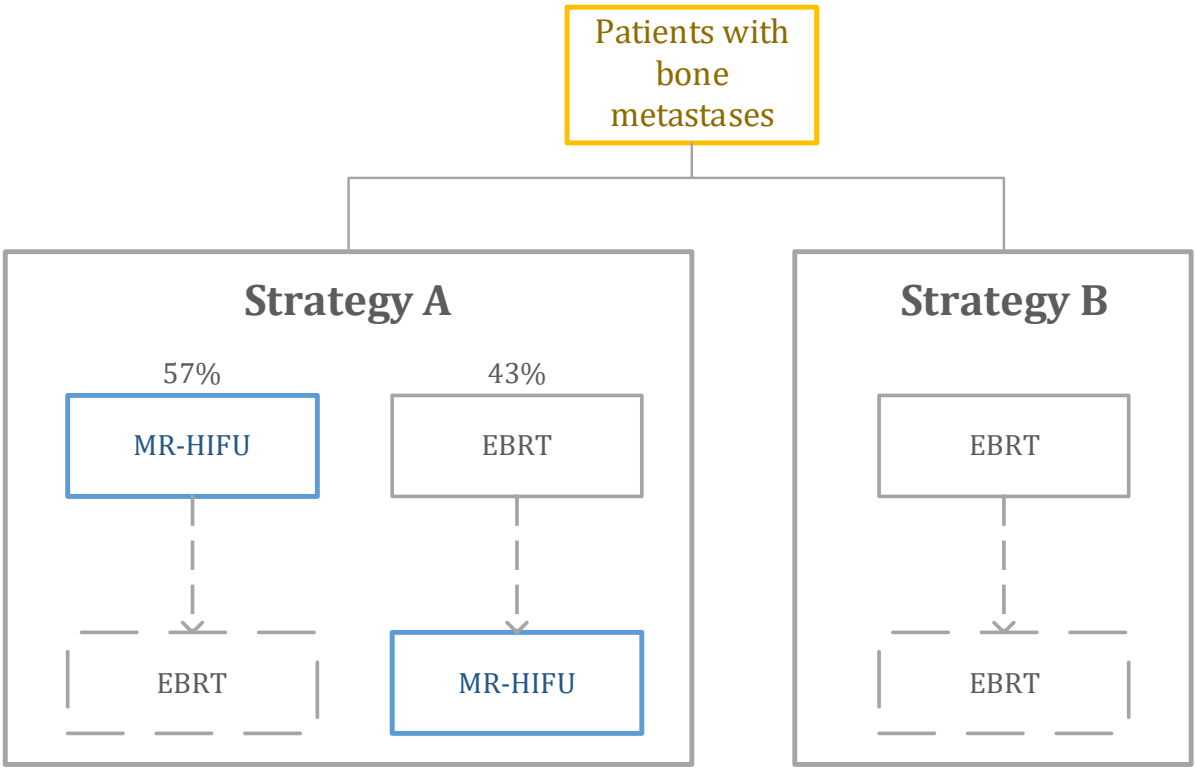


Figure 9. Strategies being compared. Dashed lines refer to the possibility of a retreatment in case of persistent pain or partial pain relief after a first-line treatment (i.e., not all patients will undergo a retreatment in their lifetime, since some patients might die, or remain with unpalliated pain for some time before being recommended a retreatment).

2.2. Model overview

The patient-level simulation model reflected the clinical course that may follow palliative treatments with MR-HIFU or EBRT: i. complete pain relief (pain score of zero in the NRS), ii. partial pain relief (i.e., defined as a reduction of pain score of at least two points without increase of analgesic intake), iii. persistent pain, iv. retreatment in case of persistent pain or pain relapse and v. death. In addition, the risk of suffering a pathological fracture was considered as an event that could occur in any health state except death, because of its economic consequences and potential impact on quality of life. Figure 10 shows the model overview.

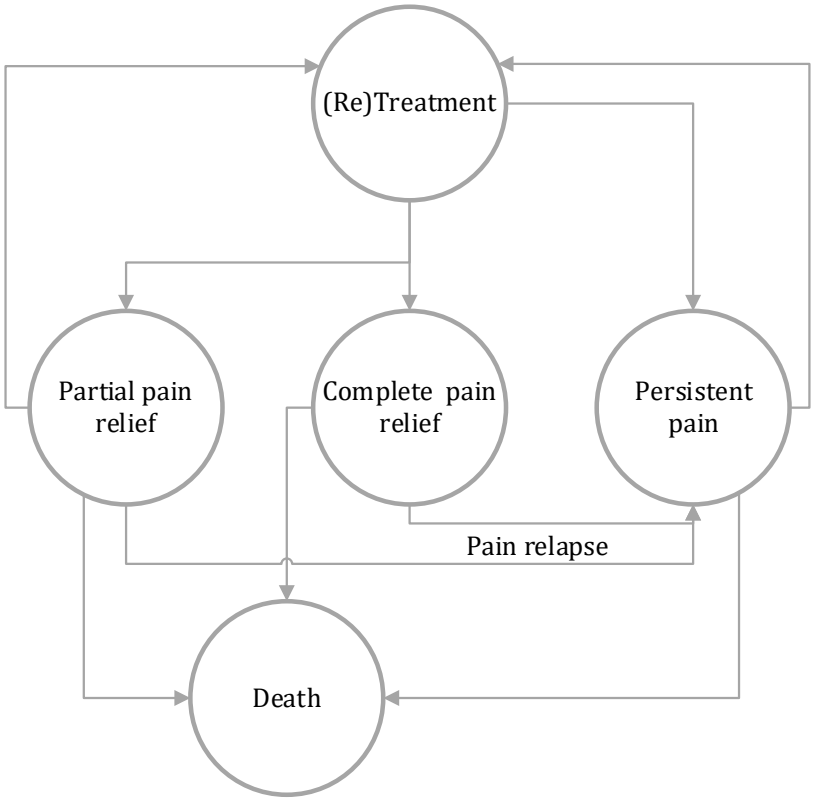


Figure 10. Model overview. Patients enter the model after treatment with either EBRT or MR-HIFU. Pathological fracture was modelled as an event that could occur in each cycle and health state (except death).

2.3. *Input parameters*

Several systematic literature searches in Medline (via PubMed) were performed to identify adequate input parameters (e.g., event probabilities, utilities, and costs). Studies were selected with regard to methodological quality and representativeness for the German context. Input parameters are reported in table 3.

Table 3. Model input parameters

Input parameter	**Value**	**Source**
Event probabilities	Monthly probability (SD)	
MR-HIFU		
Complete response (1 week after treatment)	0.230 (0.04)	(Hurwitz et al., 2014)
Partial response (1 week after treatment)	0.410 (0.04)	(Hurwitz et al., 2014)
No response (1 week after treatment)	0.350 (0.04)	(Hurwitz et al., 2014)
Retreatment	0.018 (0.0016*)	Assumption, (Rich et al., 2018)
Pathological fracture	0.003 (0.005)	(Hurwitz et al., 2014)
Multi-fraction EBRT		
Complete response (4 weeks after treatment)	0.240 (0.008)	(Rich et al., 2018)

Partial response (4 weeks after treatment)	0.380 (0.008)	(Rich et al., 2018)
No response (4 weeks after treatment)	0.380 (0.008)	(Rich et al., 2018)
Retreatment	0.007 (0.0011)	(Rich et al., 2018)
No response after retreatment	0.420 (0.021)	(Huisman et al., 2012; Rich et al., 2018)
Pathological fracture	0.003 (0.0007)	(Rich et al., 2018)
Single-fraction EBRT		
Complete response (4 weeks after treatment)	0.230 (0.008)	(Rich et al., 2018)
Partial response (4 weeks after treatment)	0.380 (0.008)	(Rich et al., 2018)
No response (4 weeks after treatment)	0.390 (0,008)	(Rich et al., 2018)
Retreatment	0.018 (0.0016)	(Rich et al., 2018)
No response after retreatment	0.420 (0.021)	(Huisman et al., 2012; Rich et al., 2018)
Pathological fracture	0.003 (0.0007)	(Rich et al., 2018)
Pain relapse in both strategies	0.022 (0.008)	(Yarnold, 1999)
Monthly probability of death after bone metastasis diagnosis		
Breast cancer	1y: 0.040(0.0004). 2y: 0.029; 3y: 0.029; 4y: 0.027; 5y: 0.027	(Schröder et al., 2017; Svensson et al., 2017)
Prostate cancer	1y: 0.053(0.0018); 2y: 0.039; 3y: 0.034; 4y: 0.029; 5y: 0.028	(Svensson et al., 2017)
Lung cancer	1y: 0.070(0.0005); 2y: 0.050; 3y: 0.050; 4y: 0.030; 5y: 0.020	(Svensson et al., 2017)
Health state utilities	QALYs adjusted for 1-month cycle (SD)	
Basic health state (painful bone metastases)	0.039 (0.035)	(Matza et al., 2014)
Pathological fracture	- 0.009 (0.021)	(Matza et al., 2014)
Multi-fraction EBRT	- 0.009 (0.025)	(Matza et al., 2014)
Single-fraction EBRT	- 0.004 (0,014)	(Matza et al., 2014)
MR-HIFU	- 0.005 (0.014)	Assumption, (Matza et al., 2014)
Complete pain relief	+ 0.019 (0.001)	(Dixon et al., 2011)
Partial pain relief	+ 0.008 (0.001)	(Dixon et al., 2011)

Costs	Value in € (SD)	
MR-HIFU		
Out-patient diagnostic MRI	118	(Hardtstock et al., 2021)
In-patient treatment (gDRG)*	3,430	(Institut für Entgeltsysteme im Krankenhaus, 2022)
MR-HIFU, cost-covering lump-sum (best- and worst-case scenarios)	5,147 (4,092–5,876)	(Simões Corrêa Galendi et al., 2022)
Multi-fraction EBRT		

Out-patient treatment*	2,411	(Kassenärztliche Bundesvereinigung, 2022)
In-patient treatment (gDRG)*	6,410	(Institut für Entgeltsysteme im Krankenhaus, 2022)
Proportion EBRT out-patient*	70%	Expert opinion, (Adamietz et al., 2002; Hechmati et al., 2013; Lievens, Kesteloot, et al., 2000)
Single-fraction EBRT	1486	(Institut für Entgeltsysteme im Krankenhaus, 2022)
Proportion of 1x 8Gy EBRT	10%	(Adamietz et al., 2002; Hechmati et al., 2013; Lievens, Kesteloot, et al., 2000)
Pathological fracture (total)	21,430 (8572)	(Hardtstock et al., 2021)
Out-patient	1,593 (637)	(Hardtstock et al., 2021)
In-patient	12,596 (5038)	(Hardtstock et al., 2021)
Rehabilitation	203 (81)	(Hardtstock et al., 2021)
Out-patient prescriptions	5,446 (2178)	(Hardtstock et al., 2021)
Aid and remedies	1,592 (637)	(Hardtstock et al., 2021)
Oxycodone 20mg each 4 hours (monthly costs)	210 (84)	(Wissenschaftliches Institut der AOK, 2022)

*Standard deviation assumed to be 20% of mean value. Abbreviations. EBRT: External Beam Radiation Therapy, MR-HIFU: Magnetic Resonance-guided High-Intensity Focused Ultrasound, MRI: Magnetic Resonance Imaging, QALY: Quality-adjusted Life Years, SD: Standard Deviation.

2.3.1. Event probabilities

Data on effectiveness of EBRT on inducing complete or partial pain palliation and risk of pathological fracture were extracted from a recently published systematic review of RCTs comparing single-fraction and multi-fraction-EBRT (Rich et al., 2018). The effectiveness of MR-HIFU for complete or partial pain relief was extracted from a RCT including 112 patients with a three-month follow up (Hurwitz et al., 2014). Effectiveness of MR-HIFU in case of upstream EBRT (strategy A) was assumed to be the same as for MR-HIFU offered as first-line treatment. Effectiveness of retreatment with the EBRT for achieving complete or partial pain relief (strategy B) was slightly inferior because there is some evidence that re-irradiation is less effective than EBRT for radiation-naive patients (Huisman et al., 2012).

Probability of pain relapse with EBRT was taken from the Bone Pain Working Party Trial, a RCT comparing multi-fraction versus single-fraction EBRT (Yarnold, 1999). This study was chosen because over 98% of patients in the multi-fraction arm were treated with a fractionation scheme similar to that used for our model (20Gy in five fractions). In this cohort, the one-year-cumulative probability of a pain relapse was 30% (Yarnold, 1999). Because of a lack of evidence for the probability of a pain relapse (resulting in retreatment after first-line treatment with MR-

HIFU), we assumed equal rates of pain relapse for MR-HIFU and EBRT, considering that recurrence of pain is mainly driven by progression of the disease (Bucknor, Chan, Matuoka, Curl, & Kahn, 2020; Yarnold, 1999).

In the literature, annual retreatment rates after multi-fraction EBRT are reported at 8%, and that after single-fraction 20% (2.5 times higher than for multi-fraction EBRT) (Rich et al., 2018). The retreatment rate after multi-fraction EBRT is lower, probably due to concerns with the cumulative radiation dose of multi-fraction EBRT, even though the time to pain increase is similar in single-fraction and multi-fraction EBRT (van der Linden et al., 2004; Yarnold, 1999). Since the retreatment rate related to MR-HIFU is unknown, in strategy A we applied the retreatment rate of single-fraction EBRT (i.e., 20% annually). The uncertainty of this assumption was tested in sensitivity analyses considering a range of retreatment rates for MR-HIFU.

Cancer-specific overall survival (OS) was obtained from a Danish population-based cohort study that included 17,251 patients with bone metastases (Svensson et al., 2017). In that study, one-year and five-year OS after diagnosis of bone metastases for patients with prostate cancer were 35% and 6%, respectively, while patients with lung cancer had a 10% one-year OS and a 1% five-year OS (Svensson et al., 2017). The OS of patients with metastasized breast cancer in that study was in line with a prospective multicenter cohort study of German patients with breast cancer metastasized to the bone (i.e., five-year OS of 22%) (Schröder et al., 2017).

2.3.2. Utilities (Quality-adjusted life years - QALYs)

Health state utility values were taken from a time trade-off study from Matza et al, which elicited utility values for patients with bone metastases and skeletal-related events (i.e., fractures and radiation to the bone) from 187 participants living in the United Kingdom (UK) and Canada (Matza et al., 2014). The increase in utility due to partial and complete pain relief were taken from a study that elicited utilities for different intensities of chronic pain (Dixon et al., 2011). The increases in utility due to complete/partial pain relief were 35% and 15% from the base state, respectively. Increases in utilities due to complete or partial pain relief were assumed to occur within seven days after MR-HIFU, and within four weeks after EBRT (Baal et al., 2021).

Utilities were subtracted due to adverse events related to treatment/retreatment and pathological fractures. Common adverse events associated with EBRT are nausea and vomiting for two weeks following treatment (Yarnold, 1999). Reported adverse events associated with MR-HIFU are discomfort or pain due to positioning, fatigue or numbness that resolve within one day after treatment (Hurwitz et al., 2014). Decreases in utilities reported for single-fraction and multi-fraction EBRT were 0.05 and 0.11, respectively (Matza et al., 2014). For MR-HIFU, data on utility has not yet been published. Hence, the utility of MR-HIFU was assumed an average of single/multi-fraction EBRT (0.07 QALY). This assumption was based on expert opinion, considering that MR-

HIFU is associated with reduced hospital time and adverse effects than multi-fraction EBRT. Compared to single-fraction EBRT, however, MR-HIFU requires general anesthesia and overnight stay which may be burdensome for patients.

2.3.3. Costs

Costs of MR-HIFU included one overnight stay at the hospital, general anesthesia and one post-treatment MRI. An additional pre-treatment out-patient MRI was considered in case MR-HIFU was performed as first-line treatment. Depending on the general condition of the patient and the total dose required, in Germany, EBRT is performed as in- or out-patient treatment. Published cost-of-illness studies and surveys indicate that the proportion of out-patient treatments in Germany is 50-60% (Adamietz et al., 2002; Hardtstock et al., 2021; Hechmati et al., 2013; Lievens et al., 2020) with no significant difference between German general hospitals, practices, and university hospitals (Adamietz et al., 2002). However, these studies assessed bone metastases in general (including complicated bone metastases, patients receiving post-operative radiation for spinal metastases, sometimes with pronounced neurological symptoms), while our patient population (uncomplicated bone metastases) is less likely to require in-patient treatment. Hence, for the base case, we assumed the proportion of out-patient EBRT to be 70% for the base case.

According to the perspective of the SHI, direct medical costs related to EBRT and MR-HIFU were based on the German Physicians' Fee Schedule 2022 (Einheitlicher Bewertungsmaßtab) for out-patient procedures (Paracha, Thuresson, Moreno, & MacGilchrist, 2016), and the 2022 German diagnosis related group (gDRG) weights (for in-patient procedures) (Peasgood, Ward, & Brazier, 2010). The diagnosis and procedure codes considered for the cost calculations are detailed on the supplementary material (SM1).

In line with similar models, for all health states except for complete pain relief, costs with pain medication were estimated considering oral oxycodone as a reference medication (Bucknor et al., 2020; Chang, Shaverdian, Capiro, Steinberg, & Raldow, 2020). For patients with persistent pain and partial pain relief, an intake of oral oxycodone 20 mg every four hours was assumed (Bucknor et al., 2020; Chang et al., 2020). For the pricing of pain medication, we referred to the German formulary 2022 (Wissenschaftliches Institut der AOK, 2022). Costs of bone targeting agents to prevent fractures (e.g., bisphosphonates) were not included because they would impact both treatment strategies equally.

Costs associated with a pathological fracture were extracted from a retrospective cost-of-illness study based on German claims data including 2434 patients with bone metastases and solid tumors (Hardtstock et al., 2021). These costs included in- and out-patient consultations, rehabilitation, out-patient prescriptions, aids, and remedies (Hardtstock et al., 2021). Costs were

adjusted for inflation to the target year 2021 based on the harmonized index of consumer price (Turner, Lauer, Tran, Teerawattananon, & Jit, 2019).

2.4. Model outputs

To compare the alternatives, the incremental cost-effectiveness ratio (ICER) was calculated as cost per pain response (i.e., months spent in complete or partial pain response) and cost per QALY. Because survival after diagnosis of bone metastasis varies by cancer type, in subgroup analyses, the ICER was calculated for each primary cancer diagnosis (i.e., breast, prostate, and lung cancer). Costs and benefits were discounted at a 3% annual rate (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2008).

2.5. Model validation and sensitivity analyses

To validate the model, we consulted experts on the adequacy of input data and the conceptual appropriateness of the model. Technical accuracy was checked regarding data entry and programming errors. For cross model validation, we compared our assumptions to those in similar models. We report the validation efforts in detail in the supplementary material (SM2), following the 'Assessment of the Validation Status of Health Economic decision models' checklist (Vemer, Corro Ramos, van Voorn, Al, & Feenstra, 2016).

In deterministic sensitivity analyses (DSA) all input parameters were varied, except for the cancer-specific mortality rates. Structural sensitivity analyses were performed to calculate the ICER considering different scenarios: i. all patients receiving MR-HIFU as first-line treatment in strategy A, ii. alternative retreatment rates in strategy A (e.g., same retreatment rates as multi-fraction EBRT and double that of single-fraction EBRT), iii. a cost-covering lump-sum for MR-HIFU, iv. a range of proportions of single-fraction EBRT (in both strategies), v. a range of proportions for out-patient EBRT (in both strategies). The cost-covering lump sum was taken from a recent time-driven activity-based costing study prospectively conducted at a university hospital from the hospital perspective (Simões Corrêa Galendi et al., 2022). The cost-covering lump sum includes capital costs for MR-HIFU equipment, which are not incorporated in the calculation of gDRG lump sums (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2008; Simões Corrêa Galendi et al., 2022).

A probabilistic sensitivity analysis (PSA) was conducted to test the robustness of the results. Because there is no commonly accepted willingness-to-pay threshold for Germany, the probability of strategy A being cost effective was assessed for different levels of willingness-to-pay (WTP) (i.e., hypothetical thresholds, at which the SHI would accept the additional costs for an additional benefit) (Woods, Revill, Sculpher, & Claxton, 2016).

2.6. Value of Information (VOI) Analysis

A VOI analysis was conducted to estimate the value of collecting additional evidence (e.g., a RCT comparing MR-HIFU with EBRT) for reducing uncertainty of the analysis (Fenwick et al., 2020). While the expected value of perfect information (EVPI) indicates whether the cost of conducting new research is worthwhile (i.e., should we collect more evidence?) (Fenwick et al., 2020), the expected value of perfect partial information (EVPPI) quantifies how individual parameters or parameters sets contribute to decision uncertainty (i.e., what evidence should we collect?) (Fenwick et al., 2020). The EVPI and the EVPPI were calculated using the Sheffield Accelerated Value of Information (SAVI) tool (Strong, Oakley, & Brennan, 2014), and epidemiologic data from the German Centre for Cancer Registry Data (Woods et al., 2016). More information is provided in the supplementary material (SM 3).

3. Results

3.1. Base case results

Compared to strategy B (EBRT alone), strategy A (with MR-HIFU) resulted in slightly higher costs (€399) and more benefits (0.02 QALYs and 0.95 months with pain response), with ICERs of €19,845 /QALY and €421 /month with pain response. Limiting the analysis to cancer-subgroups, strategy A resulted in increased costs and more benefits (breast cancer: €22,403 /QALY and €484 /pain response, prostate cancer: €21,072 /QALY and €2,281 /pain response, and lung cancer: €14,086 /QALY and €188 /pain response). Table 4 shows the results for the base case.

Table 4. Base case results and subgroup analyses according to primary diagnosis

	Cost	**Incr. Cost**	**Effectiveness**		**Incr. effectiveness**		**ICER**	
	€	€	QALY	Pain response	QALY	Pain response	€/QALY	€/Pain response
Base case								
Strategy B	8115	-	0.94	9.41	-	-	-	-
Strategy A	8514	399	0.96	10.36	0.020	0.95	19,845	421
Breast cancer								
Strategy B	9401	-	1.15	11.16	-	-	-	-
Strategy A	9852	451	1.17	12.40	0.027	1.23	22,403	484
Prostate cancer								
Strategy B	8609	-	0.95	9.64	-	-	-	-
Strategy A	8241	368	0.97	10.55	0.018	0.91	21,072	2,281
Lung cancer								

Strategy B	7417	-	0.73	7.48	-	-	-	-
Strategy A	7227	190	0.74	8.19	0.015	0.71	14,086	1,592

Strategy B: EBRT alone; strategy A: with MR-HIFU. Abbreviations. QALY: Quality-adjusted life-years gained; ICER: Incremental cost-effectiveness ratio; MR-HIFU: Magnetic resonance-guided High-Intensity Focused Ultrasound. Pain response defined as months spent with palliated pain.

3.2. DSA and structural sensitivity analyses (Table 3)

In DSA, the variables with the highest impact on the ICER were the effectiveness of MR-HIFU for complete pain relief, the retreatment rate in strategy A, the MR-HIFU treatment costs, and EBRT costs in that order. In the supplementary material (SM 4), results of DSA are shown in a tornado diagram (Figure S1).

In structural sensitivity analyses, applying alternative retreatment rates in strategy A resulted in similar results as in the base case (i.e., strategy A costs more and generates more QALY). Higher retreatment rates in strategy A resulted in higher ICERs, meaning that the more often retreatments were performed, the lesser cost effective strategy A was. Moreover, offering MR-HIFU as first-line treatment to all patients at strategy A resulted in higher additional costs (€721 vs. €364 in the base case) and slightly more QALYs (0.023 vs. 0.020 in the base case). The resulting ICER in this scenario (€31,048 /QALY) is 50% increased compared to the base case. Furthermore, structural sensitivity analyses assuming less costly EBRT practices (i.e., higher proportions of 1x8Gy dose or out-patient treatment) resulted in higher ICERs (i.e., strategy A is less likely cost effective). Complete results are provided in table S6 (in SM4).

Table 5. Structural sensitivity analyses results

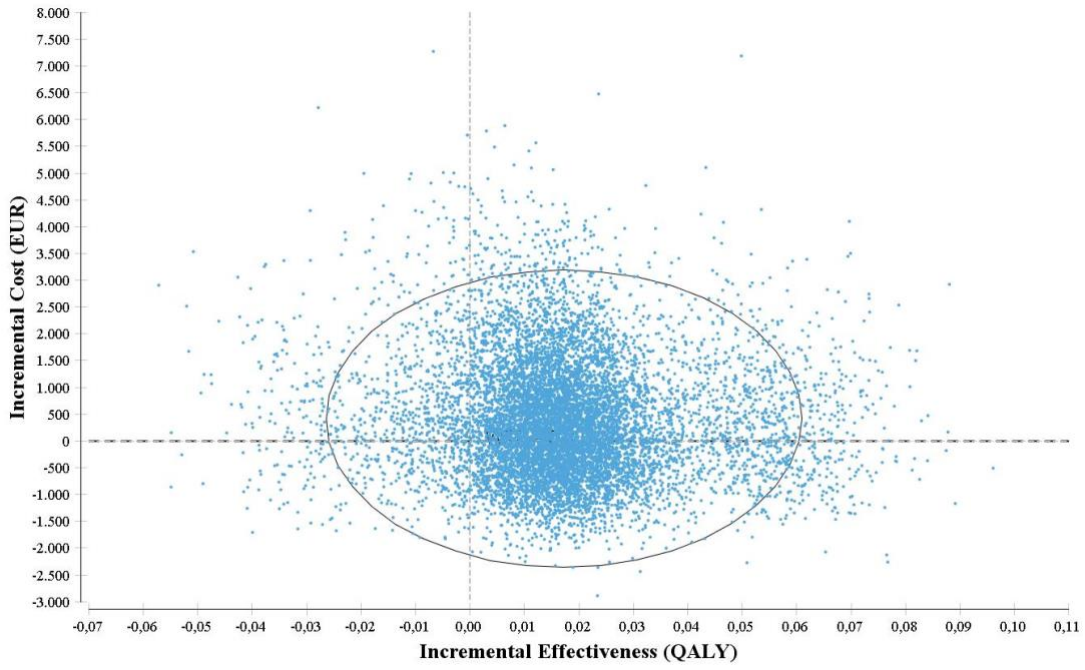
	Cost	**Incremental Cost**	**Effectiveness**	**Incremental effectiveness**	**ICER**
	€	€	QALY	QALY	€/QALY
Retreatment rate at Strategy A defined at 8% (same as MF-EBRT)					
Strategy B	8,115	-	0.94	-	-
Strategy A	8,500	385	0.96	0.02	18,531
Retreatment rate at Strategy A defined at 32% (4-fold MF-EBRT, 2-fold the base case)					
Strategy B	8,115	-	0.94	-	-
Strategy A	10,106	1,991	0.99	0.05	38,808
All patients receiving MR-HIFU as first-line treatment (at Strategy A)					
Strategy B	8,115	-	0.94	-	-
Strategy A	8,836	721	0.96	0.02	31,048
Cost-covering lump-sum MR-HIFU					
Strategy B	8115	-	0.94	-	-
Strategy A	9663	1548	0.96	0.02	77,650
All EBRT dose 1x 8Gy (at both strategies)					

Strategy B	6,214	-	0.95	-	-
Strategy A	7,388	1,174	0.96	0.01	168,392
All EBRT as out-patient treatment (at both strategies)					
Strategy B	6,604	-	0.94	-	-
Strategy A	7,742	1,138	0.96	0.02	56,566

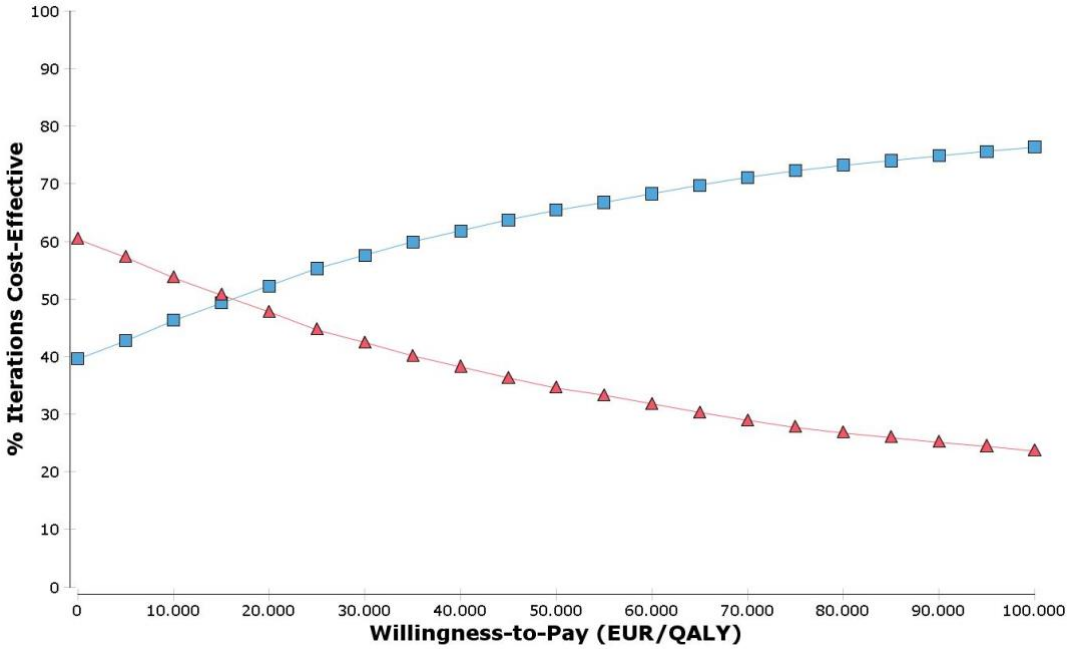
Strategy B: EBRT alone; strategy A: with MR-HIFU. Abbreviations. QALY: Quality-adjusted life-years gained; ICER: Incremental cost-effectiveness ratio; MR-HIFU: Magnetic resonance-guided High-Intensity Focused Ultrasound: MF-EBRT: Multi-fraction External Beam Radiotherapy.

3.3. PSA

In PSA, the iterations spread across the four quadrants of the cost-effectiveness plane (Figure 11A). Fifty-three percent of the iterations fall into the upper right quadrant, corresponding to the base case result (i.e., strategy A resulted in more costs and more QALYs), while 36% of the iterations fall into the lower right quadrant, indicating that strategy A may result in more QALYs and be cost saving. However, in 10% of the iterations strategy A was less effective than strategy B (upper and lower left quadrants). As a result, at a WTP of €20,000 /QALY, the probability of strategy A being cost effective is 52% (i.e., in 48% of the iterations the additional costs per QALY were above the (hypothetical) threshold of € 20,000). At a WTP of €40,000 /QALY, the probability of strategy A being cost effective is 64% and at €60,000 /QALY, 69%. Figure 11B shows the cost-effectiveness acceptability curve for a range of willingness-to-pay values.



A



B

Figure 11. Results of probabilistic sensitivity analysis. (A) Incremental cost-effectiveness plane with 10.000 iterations resulting from probabilistic sensitivity analysis with 95% confidence ellipse; (B) Cost-effectiveness acceptability curve for a range of willingness-to-pay values. Strategy A indicated in blue and strategy B in red.

3.4. VOI Analysis

The EVPI for the choice between strategy A and strategy B was €434 /person affected by the decision. Extrapolated to the German population over a period of five years, the EVPI was €178 Mio. These values represent the cost of making the decision based on current (uncertain) evidence and set the maximum amount that should be applied into additional research to reduce uncertainty of the analysis. The parameters with the highest EVPPI per person were MR-HIFU costs (329, SD:5) and the fracture rate following MR-HIFU (151; SD: 8). Further relevant parameter sets worthy of collecting further information were: QALY values (67, SD: 4), proportion of single-fraction and of out-patient EBRT jointly (EU 62, SD: 6) and effectiveness of MR-HIFU on pain palliation (53, SD: 6), as detailed on the supplementary material (SM 5).

4. Discussion

In comparison to EBRT, the MR-HIFU strategy resulted in higher costs and more benefits (QALYs and months of pain response) for patients with bone metastases. The overall results were confirmed in subgroup analyses for breast cancer, prostate cancer, and lung cancer. Patients with bone metastases due to lung cancer had the lowest lifetime (cumulative) costs and benefits, probably because 90% of these patients died within the first year. Because the added benefit of MR-HIFU is short-term (i.e., faster pain relief than EBRT) and the most impactful additional costs

are long-term (i.e., costs of retreatment and fracture), strategy A was more cost effective for this subgroup of patients with poorer prognosis. While the German SHI cannot expect savings with MR-HIFU, the cost-effectiveness was similar to various medical interventions for bone metastases (Andronis, Goranitis, Bayliss, & Duarte, 2018).

Due to a lack of appropriate data (e.g., a direct clinical comparison between the treatment alternatives) the model had to be based on different clinical studies several assumptions. As a result, at a WTP of €20,000 /QALY, the probability of MR-HIFU being cost effective is 52%, whereas for a WTP of €60,000 /QALY the probability is 69%. In Germany, there is not a commonly accepted WTP threshold to determine reimbursement decisions. For WTP thresholds higher than €20,000 /QALY, the potential cost-effectiveness might justify investments in infrastructure installation. Moreover, early economic models are useful to explore (i) MR-HIFU's role in the clinical management of bone metastases and (ii) the potential value of further research (Grutters et al., 2019; Love-Koh, 2020).

Because the role of MR-HIFU in the clinical management of painful bone metastases is still incipient, we explored several alternative scenarios in structural sensitivity analyses. For example, it was detectable that higher retreatment rates at strategy A tend to increase the ICER. Furthermore, a scenario with MR-HIFU being offered as first-line treatment for all patients increased the ICER (€31,048 /QALY), due to a higher increase in costs despite a slight increase in QALYs. Although not considered in our calculations, some case series indicate that patients without prior radiation might respond better to MR-HIFU than those with prior radiation (Baal et al., 2021; Han, Huang, Meng, Yin, & Song, 2021). The mechanism of action supporting this finding warrants further investigation. If this early evidence from case series is confirmed in larger samples, the cost-effectiveness of MR-HIFU as first-line treatment would be improved.

Repeated irradiations from EBRT are limited due to normal tissue tolerance (Lievens, Kesteloot, et al., 2000; van der Linden et al., 2004). In contrast, MR-HIFU could be repeated for non-responders since there is theoretically no limit for the accrued acoustic energy (Baal et al., 2021; Huisman et al., 2015). However, the possibility of repeating MR-HIFU (i.e., MR-HIFU after initial treatment with MR-HIFU) was not considered in this model, because to date there is not sufficient clinical data on the effectiveness and safety of repeating MR-HIFU (Baal et al., 2021; Han et al., 2021). Moreover, long-term outcomes of repeating MR-HIFU such as risk of pathological fracture, duration of pain response, retreatment rates are unknown in this early phase of implementation. The alternative of repeating MR-HIFU should be investigated in future models once further evidence becomes available.

The high populational EVPI (approximately €180 Mio.) indicates that further studies would be worthwhile for reducing uncertainty (Fenwick et al., 2020). Moreover, the EVPPI enabled us to identify parameters that contribute most to decision uncertainty (i.e., MR-HIFU

costs and fracture rates after MR-HIFU). An ongoing randomized controlled trial comparing MR-HIFU with either EBRT or a combination of both is currently recruiting patients with painful bone metastases (Clinical.trials.gov registration number NCT04307914). The results of this trial may clarify most of the uncertainty around patient relevant outcomes, especially the effectiveness in pain palliation.

In addition to the primary goal of pain palliation, a technology's ability to induce local tumor control may contribute to the prevention of pathological fractures (Huisman et al., 2015). Currently, data on local tumor control is based on stronger evidence for EBRT than for MR-HIFU. For instance, in our model, fracture rates for EBRT were taken from a large meta-analysis with 2,468 patients (Rich et al., 2018), while the source of fracture rate for MR-HIFU was limited to an RCT with 112 patients (Hurwitz et al., 2014), resulting in larger standard deviations for MR-HIFU and high EVPPI for MR-HIFU-related fracture rates. Preclinical evidence shows that MR-HIFU neither compromises the mechanical function of bones nor cause micro-cracks at the bone tissue level (Yeo et al., 2015). However, improved evidence on fracture rates would be relevant for the cost-effectiveness of MR-HIFU and might be achieved by establishing prospective registries with the opportunity of embedded clinical trials.

Some limitations should be acknowledged. Firstly, choosing multi-fraction EBRT as the preferred comparator for our model may limit the generalizability of the results to other settings (van der Linden, Roos, Lutz, & Fairchild, 2009). The preference for single-fraction EBRT in many health systems may be justified by evidence on equivalent pain palliation and local tumor control, requirements to optimize machine availability and lower costs (Rodin et al., 2021; van der Linden et al., 2009). However, in Germany the fee-for-service reimbursement schemes seem to favor multi-fractionated schemes for radiotherapy practices (Lievens, Van den Bogaert, Rijnders, Kutcher, & Kesteloot, 2000), what in conjunction to physicians' preferences, slows down the international trend toward hypo-fractionated schemes (Popovic et al., 2014). Hence, our choice of comparator in the base case reflected EBRT practice in Germany (Adamietz et al., 2002; Lievens, Kesteloot, et al., 2000), and the recommendations from the German guideline on supportive therapies for oncologic patients (Leitlinienprogramm Onkologie, 2017). Additionally, in sensitivity analyses we explored the impact of different EBRT practices.

Secondly, costs with transportation to out-patient radiotherapy treatment are partially reimbursed but were excluded from our analysis due to lack of data. Nevertheless, transportation costs were expected to be very low (i.e., calculated as €0.20 / km, and accounting for a fixed co-pay of €5 to €10), hence the impact on model outputs are likely to be negligible. Thirdly, cancer patients can opt for rehabilitation after treatment with EBRT or MR-HIFU. Costs due to rehabilitation were not included in the analysis, because these costs are expected to incur in both

groups. Moreover, costs with oncologic rehabilitation are commonly reimbursed by the German Pension Insurance.

Finally, although the clinical impact of adverse events on QALYs were accounted for, the corresponding costs associated with diagnosing and treating adverse events were not included. For example, 40% of patients treated with EBRT need symptomatic medication for nausea and vomiting for the first two weeks (Yarnold, 1999). However, the related costs (e.g., for anti-sickness tablets) are modest, and for MR-HIFU adverse events are reported in only 1% of the patients (Hurwitz et al., 2014). Moreover, most adverse events related to MR-HIFU (e.g., discomfort or pain due to positioning, fatigue, numbness) are resolved prior to discharge with no need of additional diagnostic or treatment procedures (Hurwitz et al., 2014). Hence, costs related to adverse events are unlikely to impact the model results.

Similar to our model, a previous cost-effectiveness Markov model from the U.S. showed that MR-HIFU results in both additional costs and QALYs, yielding an ICER of $54,160 /QALY (Bucknor et al., 2020). However, because this model compared MR-HIFU with medication only, the comparability to our model results is limited. Our model is the first to compare a MR-HIFU-based strategy with EBRT, which is the current standard care. Moreover, the VOI analyses offers a refined information to decision-makers, highlighting the value of collecting more evidence on MR-HIFU to optimize health outcomes for patients with bone metastases.

5. Conclusion

In summary, for patients with bone metastases the MR-HIFU-based strategy resulted in moderately higher costs and benefits in terms of both QALY (which accounted for adverse events of both treatments) and pain response compared to EBRT alone. Although there is still considerable uncertainty around the model results, this analysis can inform research prioritization, support decisions about reimbursement, and investments in infrastructure installation. Once further evidence is available, an updated economic modelling study would be opportune.

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Chapter VI

Factors influencing the adoption of MR-HIFU for painful bone metastases in Europe: a Group Concept Mapping Study

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- Institutional Review Board Statement: Ethical review and approval were waived for this study because no personal information was collected, and data is not considered sensitive or confidential in nature.

- Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

- Data Availability Statement: The data presented in this study are available in the article and supplementary material.

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Abstract

Magnetic resonance imaging-guided high-intensity focused ultrasound (MR-HIFU) is an innovative treatment for patients with painful bone metastases. The adoption of MR-HIFU will be influenced by several factors beyond its effectiveness. To identify contextual factors affecting the adoption of MR-HIFU, we conducted a Group Concept Mapping (GCM) study in four European countries. The GCM was conducted in two phases. First, participants brainstormed statements guided by a focus prompt "One factor that may influence the uptake of MR-HIFU in clinical practice is...". Second, participants sorted statements into categories; and rated the statements according to their importance and changeability. To generate a concept map, multidimensional scaling and cluster analysis were conducted, and average ratings for each (cluster of) factors were calculated. Forty-five participants contributed to phase I and/or II (56% overall participation rate). The resulting concept map comprises 49 factors, organized in 12 clusters: 'competitive treatments', 'physicians' attitudes', 'alignment of resources', 'logistics and workflow', 'technical disadvantages', 'radiotherapy as first-line therapy', 'aggregating knowledge & improving awareness', 'clinical effectiveness', 'patients' preferences', 'reimbursement', 'cost-effectiveness' and 'hospital costs'. The factors identified echo those from literature, but their relevance and interrelationship are case-specific. Besides evidence on clinical effectiveness, contextual factors from 10 other clusters should be addressed to support adoption of MR-HIFU.

Keywords: MR-HIFU; bone metastases; cancer pain; implementation science; diffusion of innovation; group concept mapping.

1. Introduction

Pain is a common consequence of bone metastases that substantially reduces the quality of life of patients with advanced cancer (Mantyh, 2014; Paice & Ferrell, 2011). For patients with persistent pain despite the use of analgesics, radiotherapy is a well-established treatment option that leads to complete or partial pain relief after two to four weeks in about 60-70% of patients (Chow et al., 2014; Rich et al., 2018; van der Linden et al., 2004). Magnetic resonance image-guided high-Intensity focused ultrasound (MR-HIFU) is an emerging non-invasive alternative that holds the promise to promote faster pain palliation than radiotherapy in a larger proportion of patients (Baal et al., 2021; Han, Huang, Meng, Yin, & Song, 2021; Huisman et al., 2015).

HIFU thermally ablates the periosteal nerve and tumor by delivering acoustic energy to the targeted treatment region (Scipione et al., 2018). HIFU can be performed under the guidance of magnetic resonance imaging (MRI) or ultrasound, but MRI guidance is preferred for bone treatments because MRI thermometry provides a near real-time assessment of temperature and thermal-dose distribution on soft tissues (Scipione et al., 2018). This enables monitoring the thermal damage on the treated and surrounding healthy tissues, and modulation of the energy level in case the temperature rise is insufficient (Scipione et al., 2018). MR-HIFU can be performed under general anesthesia or sedation depending on the location of the treatment, the patient characteristics, and the experience of the attending physicians, and it therefore requires an anesthesiologist or sedationist in the MRI room during the procedure (Simões Corrêa Galendi et al., 2022).

After MR-HIFU treatment, pain response occurs within three days, and 67% to 88% of patients have complete or partial pain relief (Baal et al., 2021; Han et al., 2021; Hurwitz et al., 2014). To date, no randomized controlled trial (RCT) has been performed to compare the effectiveness of MR-HIFU to radiotherapy. Therefore, a three-armed RCT was designed, to compare focused ultrasound and radiotherapy for noninvasive palliative pain treatment in patients with bone metastases – the FURTHER-trial (ClinicalTrials.gov Identifier: NCT04307914).

Evidence from RCTs should underpin the adoption of medical technologies in medical settings, including oncology (Urquhart et al., 2019). However, the adoption of medical technologies encompasses multiple interacting factors, such as the patient's experience with the underlying illness, the clinician's resistance to new technologies, the processes of technology application in organizations, financing, and regulatory aspects (Greenhalgh et al., 2018). These contextual factors have proven to play an even stronger role in the adoption of new technologies than the proof of their effectiveness (Urquhart et al., 2019).

Thus, to understand the complexity of the interventions, and the complexity of the social context in which interventions are being tested, qualitative research is increasingly undertaken

alongside RCTs (O'Cathain, Thomas, Drabble, Rudolph, & Hewison, 2013). This is necessary because effectiveness or efficacy RCTs tolerate or control the context but do not engage with it from different perspectives. Besides, to support the implementation of new technologies, barriers and facilitators from different levels and contexts need to be elicited in order to ground the development of effective implementation strategies (Bauer & Kirchner, 2020). The most common methodologies applied to elicit contextual factors on various levels are focus groups, semi-structured interviews or mix-method research such as Delphi panels (O'Cathain et al., 2013). Group concept mapping (GCM) is one alternative participatory mixed-method research that has been applied to theory development, planning of programs and social interventions, and evaluation of programs in healthcare (Trochim & Kane, 1989).

The adoption of MR-HIFU technology is expected to face several challenges, including technical advancements, accumulation of clinical evidence and reimbursement (Foley et al., 2013). However, a systematic evaluation of barriers and facilitators influencing the adoption of MR-HIFU for bone metastases was lacking. To investigate barriers and facilitators influencing the adoption of MR-HIFU in European countries, a GCM approach was applied alongside the FURTHER-trial. Our objective was to elicit the contextual factors influencing the adoption of MR-HIFU, which are not routinely addressed in the RCT design, but could equally impact successful adoption of this technology.

2. Materials and Methods

2.1. Study settings

FURTHER is a H2020 funded research project that aims to assess the effectiveness of MR-HIFU to improve early pain palliation for cancer patients with painful bone metastases. The FURTHER project's main component is a prospective, multicentric, three-arm RCT (ClinicalTrials.gov registration number NCT04307914); the first to assess the effectiveness of MR-HIFU compared to either radiotherapy or a combination of MR-HIFU and radiotherapy for pain palliation. Patient recruitment for the trial started on 10.03.2020 in the Netherlands, Germany, Finland, and Italy (Bartels, 2021). The GCM study took place in an early phase of the FURTHER-trial.

2.2. GCM

GCM combines qualitative data obtained from participatory inquiry and multivariate statistical analyses to create concept maps. These concept maps are visual representations that summarize the main ideas of the group (i.e., representing multiple perspectives) and their interrelationships (Rosas, 2017; Trochim & Kane, 2005). The resulting concept maps express the

opinion of the participants on the topic using their own terms and can then be used as a guide for strategically planning the adoption of medical technologies (Rosas, 2017; Trochim & Kane, 1989).

2.3. Participant selection of the GCM study

Participants represented different perspectives: patients, referring physicians, medical specialists, clinical researchers, technology providers, hospital managers, including members of the FURTHER Consortium. Participants were selected using two different methods. First, purposive sampling was used to ensure diverse representation (Valerio et al., 2016). Second, snowball sampling (i.e., a chain-referral method) was used to facilitate participant engagement (Valerio et al., 2016).

An invitation letter was sent via email to all identified stakeholders outlining the purpose of the GCM study. The invitation letter included a link to the FURTHER project website, where information on MR-HIFU procedure and the FURTHER project was available. A link was provided at the end of the letter, and those interested in participating created a username and password. A similar invitation was sent before the beginning of phase I and phase II and participation in phase II was independent from phase I.

2.4. Data collection and analysis

Data collection was conducted online using the platform from Group Wisdom™ (Concept System Inc, Version 2020). At first login, participants signed electronically an informed consent (provided in supplementary material – SM1) and were informed that they could withdraw consent for participation anytime. Participants' anonymity was guaranteed, and they were asked three to five non-identifying questions about their own background to allow subgroup analyses (SM1).

The GCM study was then conducted in two phases: phase I consisted of a brainstorming task, and phase II comprised sorting and rating tasks. The tasks were conducted in English, with the objective of engaging all countries in creating a single European concept map. Figure 12 summarizes the tasks presented to each participant in each phase and how the data was processed and analyzed.

2.4.1. Phase I – Brainstorming

Phase I took place from August 1st to December 31st, 2021. During this period, participants were asked to brainstorm statements guided by a focus prompt. The focus prompt reflected the research question in a complete-the-sentence format: "One factor that may influence (either positively or negatively) the uptake of MR-HIFU in clinical practice in my country or local context is that..." Reminders were sent by email monthly encouraging participants to add new statements and to complement the ideas from other participants gathered during that period. Phase I was

stopped when the topic was exhausted (i.e., if one week after the last reminder, participants stopped adding new statements).

To eliminate redundancy and potential ambiguity, the statements added were processed. Two researchers (JSCG and ACS) followed a stepwise approach: (i) splitting statements with more than one idea; (ii) merging redundant statements; (iii) editing the remaining statements to ensure comprehensibility. Finally, one participant revised the resulting list of statements to ensure there was no data loss or change in meaning.

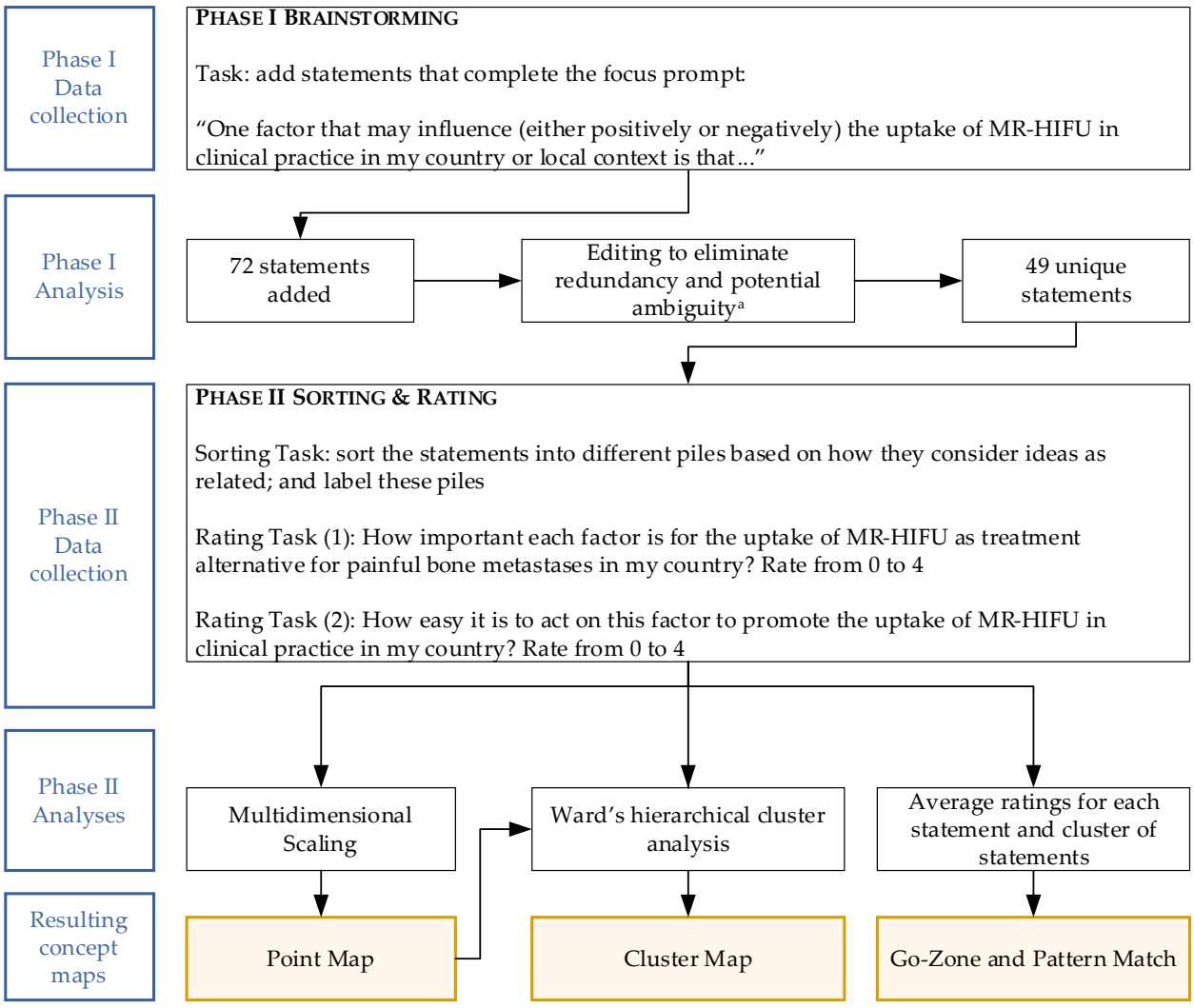

Figure 12. Overview of data collection and analysis for the GCM Study. Participants are responsible for generating ideas (phase I) and organizing and structuring the ideas (phase II). a Performed by two researchers independently.

2.4.2. Phase II – Sorting and Rating

Phase II took place from April 12th to May 31st, 2022, and reminders were sent every two weeks. Participants had the choice to log out and resume as many times as needed until the

predefined end date of Phase II. The statements were presented in a random order for the participants to complete two tasks: sorting and rating the statements.

First, participants were asked to sort the statements into different piles based on how they consider ideas to be related; and label these piles. Participants were explicitly instructed not to sort statements according to priority or value (e.g., important, hard-to-do) and not to group dissimilar statements into an indefinite pillar (e.g., labeled 'other').

Second, participants were asked to rate statements on two dimensions: (i) Importance (i.e., how important is this factor for the uptake of MR-HIFU treatment for bone metastases in your country?), and (ii) Changeability (i.e., how possible is it to act on this factor to promote the adoption of MR-HIFU for bone metastases in your country?). To answer both questions, each statement was rated using five-point Likert scales, from zero (not at all important/not at all possible) to four (extremely important/extremely possible).

Data generated in phase II were analyzed using the GCM software (Concept System Inc, Version 2020). To generate the point map, multidimensional scaling (MDS) was used to attribute X-Y coordinates to the statements, which were then plotted into a two-dimensional plane. To understand the cohesiveness between statements, bridging indices were calculated (on a zero to one scale). Bridging indices closer to zero indicates that a statement was often piled together with statements immediately adjacent to it on the map. Finally, we calculated the stress value for the study. The stress value reflects the discrepancy between the input data matrix (i.e., the original sorting data) and the final point map (SM 2) (Cox & Cox, 2008). Stress values of previous GCM studies ranged between 0.205 and 0.365. Thus, having a lower stress value than the average of previous studies (0.285) indicates that the participants sorted the statements in a similar manner (Rosas, 2017; Trochim & Kane, 2005).

To develop the cluster map, Ward's hierarchical cluster analysis was applied to group statements reflecting similar concepts into clusters. To decide on the final number of clusters, two researchers (ACS and JSCG) independently examined several cluster solutions (from 15 to six). Starting with the 15-cluster solution, the clusters were merged one by one until information was lost which could impact the practicality or interpretability of the cluster map. Bridging indexes were considered whilst constructing the cluster map, and labels derived from the original sort data. A closing session was organized in a hybrid event with all authors to finalize the labeling of the clusters (in cases where a clear preference from the original sort data could not be identified).

Furthermore, we calculated average ratings for each statement and cluster of statements. Average rating values were plotted in pattern matches to show how clusters were ranked according to importance and changeability. Average ratings were plotted in go-zone displays (i.e., bi-variate graphs for two rating dimensions - importance and changeability). The Go-Zone is divided into four quadrants (above and below the mean rating for each dimension). Statements

falling at the northeast quadrant are important statements, on which it is possible to act, and therefore should be prioritized. The Pearson's correlation coefficient was calculated to measure the linear relationship between the two rating dimensions. Lastly, subgroup analyses were performed per country, and we calculated the variance of average ratings to determine the coherence between country subgroups.

3. Results

3.1. Participants

Overall, 79 stakeholders were invited, and 45 of them were involved in at least one phase of the study, resulting in a participation rate of 56%. In phase I, 28 (35%) participants contributed to the brainstorming task. In phase II, 31 (39%) contributed to the sorting task, 33 (41%) rated statements according to importance and 29 (36%) according to changeability. Table 6 shows the participants' characteristics according to each phase of the study.

Table 6. Participants' characteristics

	Phase I	**Phase II**			**All Phases**
	Brain-storming	**Sorting**	**Rating Importance**	**Rating Changeabi-lity**	**All tasks**
Participants	28	31	33	29	45
Member of the FURTHER consortium?					
yes	24 (86%)	24 (71%)	23 (70%)	19 (66%)	32 (71%)
no	4 (14%)	10 (29%)	10 (30%)	10 (34%)	13 (28%)
Per country					
Germany	6 (21%)	7 (21%)	7 (21%)	6 (19%)	9 (20%)
Finland	4 (14%)	6 (18%)	6 (18%)	6 (19%)	7 (16%)
Italy	5 (18%)	11 (32%)	11 (33%)	10 (34%)	12 (27%)
Netherlands	11 (39%)	10 (29%)	9 (27%)	7 (24%)	15 (33%)
Other	2 (7%)	0	0	0	2 (4%)
Expertise in relation to the MR-HIFU provision					
Patient	1 (4%)	0	0	0	1 (4%)
Expertise on performing HIFU treatment	9 (32%)	10 (29%)	10 (30%)	7 (24%)	14 (34%)
Expertise on other medical specialties	9 (32%)	14 (41%)	14 (42%)	14 (48%)	19 (42%)
Expertise on the HIFU technology	7 (25%)	8 (24%)	7 (21%)	6 (21%)	9 (20 %)
Expertise on the Value Proposition/ Financial aspects	2 (7%)	2 (6%)	2 (6%)	2 (7%)	2 (4%)

Self-perceived knowledge on MR-HIFU latest evidence					
Excellent	8 (29%)	6 (18%)	5 (15%)	4 (14%)	9 (20%)
Good	12 (43%)	16 (47%)	16 (48%)	14 (48%)	19 (42%)
Regular	5 (18%)	6 (18%)	6 (18%)	5 (17%)	9 (20%)
Low	2 (7%)	6 (18%)	6 (18%)	6 (21%)	7 (16%)

Abbreviation. MR-HIFU: Magnetic Resonance-Image Guided High-Intensity Focused Ultrasound.

3.2. Collected statements

Seventy-one statements were collected at the end of phase I. Monthly reminders were useful especially because when participants logged in a second time, they could read and complement the statements added by other participants. For example, one participant added the statement 'reimbursement'; in a second login other participants complemented with the statements 'Reimbursement in ambulatory care is essential', and 'Reimbursement is important, both inside the hospital and in ambulatory care'.

After adjusting for redundancy and potential ambiguity, 49 statements entered phase II to be sorted and rated. In the SM3, figure 1A and table 2A detail and exemplify the process of splitting and merging statements.

3.3. Concept maps

Sorting data from 28 participants entered the MDS and cluster analysis. Three participants had to be excluded because they sorted most statements according to priority (e.g., don't agree, important) or value (i.e., two piles of positive vs. negative factors).

The point map (figure 2A in SM4) shows the statements (and respective identification numbers) plotted on an x–y chart. The calculated stress value was 0.2560. The cluster map (figure 13) comprised of 12 clusters: 'competitive treatments', 'physicians' attitudes', 'alignment of resources', 'logistics and workflow', 'technical disadvantages', 'radiotherapy as first-line therapy', 'aggregating knowledge & improving awareness', 'clinical effectiveness', 'patients' preferences', 'reimbursement', 'cost-effectiveness' and 'hospital costs'. Table 2 illustrates one representative statement for each cluster, and a full list of the statements contained in each cluster is provided in the supplementary material (SM5).

To ensure internal validity, one adjustment in the clusters had to be made. According to the initial hierarchical cluster analysis, statement 14 (i.e., "difficult patient recruitment, due to a large range in referring medical specialists") was assigned to cluster 'radiotherapy as first-line therapy'. However, bridging values indicated that statement 14 was often piled with statements from clusters 'physicians' attitude' and 'logistics and workflow'. Because statement 14 matched the issue addressed in cluster 'physicians' attitude' more appropriately, it was manually moved to this cluster.

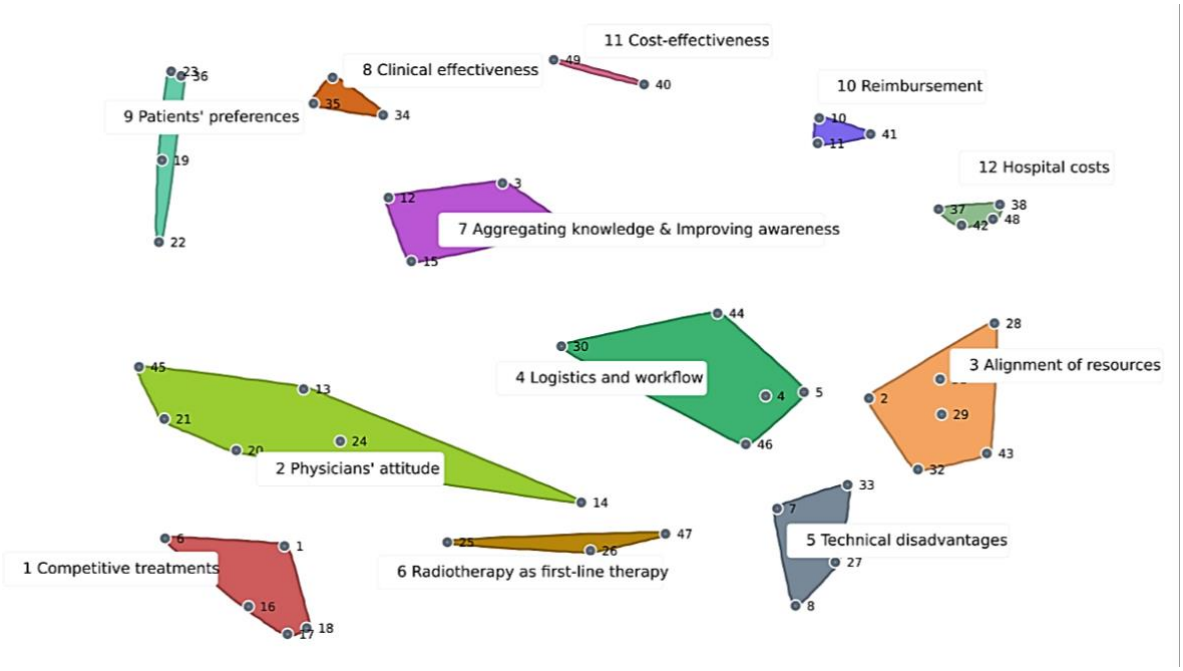

Figure 13. Cluster Map. Statements are numbered and represented by dots. The closer the statements are to each other, the more often they were sorted together by participants.

Table 7. Representative statements for each cluster

Cluster		**Statements**	
ID number	**Caption**	**ID number**	**Representative statement (ID)**
1	Competitive treatments	6	Availability of ultrasound-guided HIFU as a competitive treatment alternative
2	Physicians' attitude	13	Unfamiliarity among referring physicians with MR-HIFU as a treatment option
3	Alignment of resources	31	Frequency of time slots at the MRI dedicated for HIFU
4	Logistics and workflow	46	Lack of an established patient workflow (from HIFU-indication to release of the patient)
5	Technical disadvantages	7	MR-HIFU is a lengthy procedure
6	Radiotherapy as first-line therapy	25	HIFU is less flexible with respect to different anatomical regions compared to radiotherapy
7	Aggregating knowledge & Improving awareness	12	Clear position of MR-HIFU in clinical guidelines
8	Clinical effectiveness	34	Clinical evidence from randomized clinical trials on the effectiveness of MR-HIFU
9	Patients' preferences	19	Enthusiasm for the non-invasive treatment

10	Reimbursement	10	Reimbursement of MR-HIFU as inpatient procedure
11	Cost-effectiveness and	40	Evidence on cost-effectiveness in relation to standard of care
12	Hospital Costs	48	Costs of initial setup (purchase of equipment, installation, etc.)

3.3.1. Importance and changeability of statements and clusters

Pattern matches show the differences between the two rating dimensions (importance vs. changeability) (Figure 14). Cluster 'clinical effectiveness' was the most important and the most changeable, while cluster 'competitive treatments' was the least important and the least changeable.

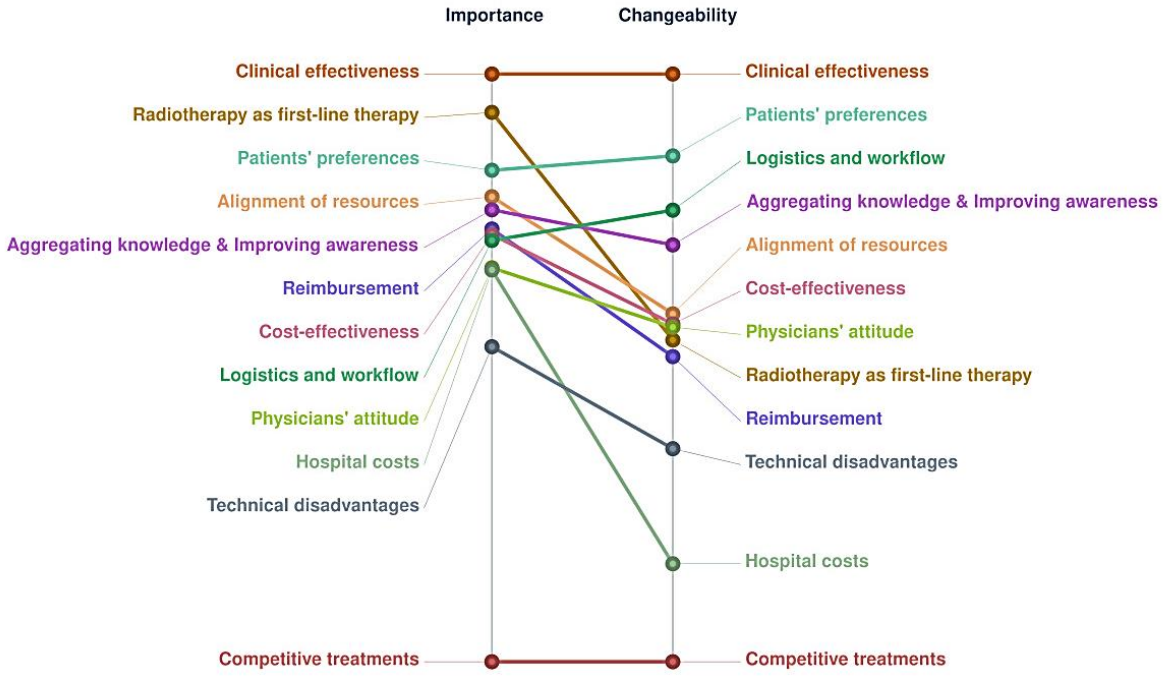

Figure 14. Comparison of the two rating dimensions, importance vs. changeability of clusters. Pattern matches show the average rating value (calculated from Likert scales ranging from 0 to 4), considering results from all participants.

Cluster 'clinical effectiveness' was the most important, followed by 'radiotherapy as first-line therapy' and 'patients' preferences'. The coherence of perceived importance was notably lower for cluster 'reimbursement' and 'clinical effectiveness' (i.e., variance between countries 0.34 and 0.14, respectively). Table 8 shows the clusters ranked in order of importance.

Table 8. Clusters ranked in order of importance and coherence between countries

Cluster ID	Cluster	Average perceived importance	Coherence of perception between countries [a]
8	Clinical effectiveness	2.99	0.14
6	Radiotherapy as first-line therapy	2.89	0.03
9	Patients' preferences	2.73	0.03
3	Alignment of resources	2.65	0.08
7	Aggregating knowledge & Improving awareness	2.62	0.00
10	Reimbursement	2.56	0.34
11	Cost-effectiveness	2.55	0.02
4	Logistics and workflow	2.53	0.02
2	Physicians' attitude	2.45	0.02
12	Hospital costs	2.45	0.05
5	Technical disadvantages	2.24	0.03

[a] Higher variance values reflect lower coherence among countries.

For the cluster 'reimbursement', average importance ratings were higher for Germany and the Netherlands (average ratings ≥3.00) compared to Italy (average 2.33) and Finland (average 1.83). The low coherence between countries regarding importance of cluster 'clinical effectiveness' was explained by divergence in one country. Figure 15 shows average ratings on the importance dimension according to country-specific subgroups. In Italy the most important factors were the availability of anesthesiologists for MR-HIFU procedures (statement 43) and frequency of time slots at the MRI dedicated for HIFU (statement 31), both from cluster 'alignment of resources'.

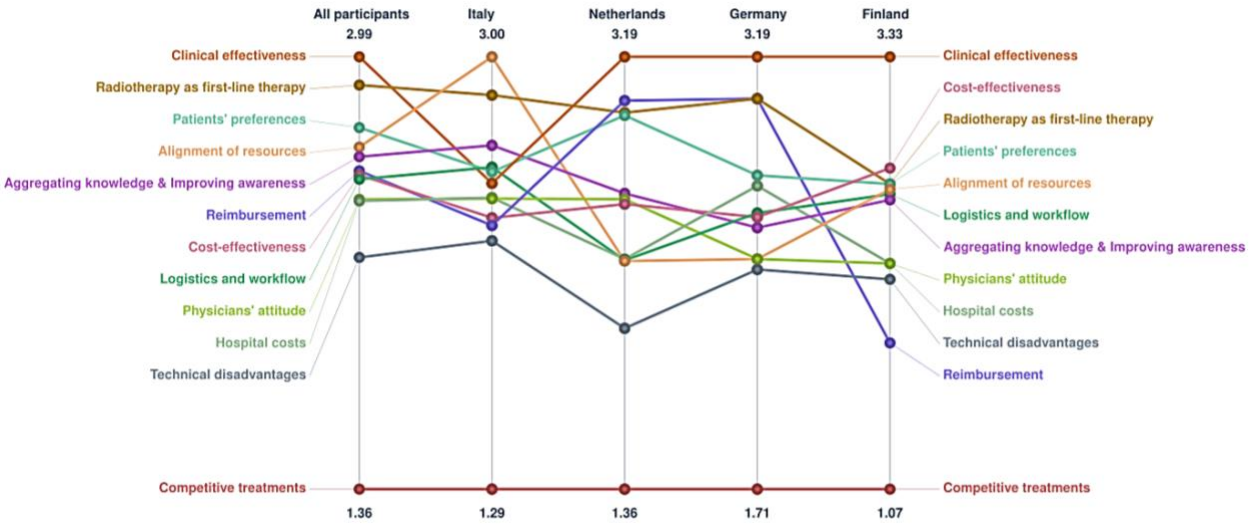

Figure 15. Importance of clusters per country-subgroup. Pattern matches show the average rating value (calculated from Likert scales ranging from zero to four).

On the statement level, the factors perceived as most important were: 34 – "clinical evidence from randomized clinical trials on the effectiveness of MR-HIFU" (average rating: 3.22); 12 – "clear position of HIFU in clinical guidelines" (average rating: 3.18); and 43 – "availability of anesthesiologists for MR-HIFU procedures" (average rating: 3.13). Average ratings for all statements are provided in the supplementary material (SM4).

Figure 16 shows average ratings for how important the statements are, and how possible it is to act on each statement to promote the adoption of MR-HIFU. The correlation between the two rating dimensions was high (r=0.77), resulting in 22 (44%) statements falling at the northeast quadrant (i.e., important statements, on which it is possible to act). Notably, all statements contained in clusters 'clinical effectiveness' and 'patients' preferences' fell into the northeast quadrant. At least one factor from 8 other clusters (including 'physicians attitudes', 'alignment of resources', 'logistics and workflow', 'technical disadvantages', 'radiotherapy as first-line therapy', 'aggregating knowledge & improving awareness', 'reimbursement', and 'cost-effectiveness') fell into the northeast quadrant.

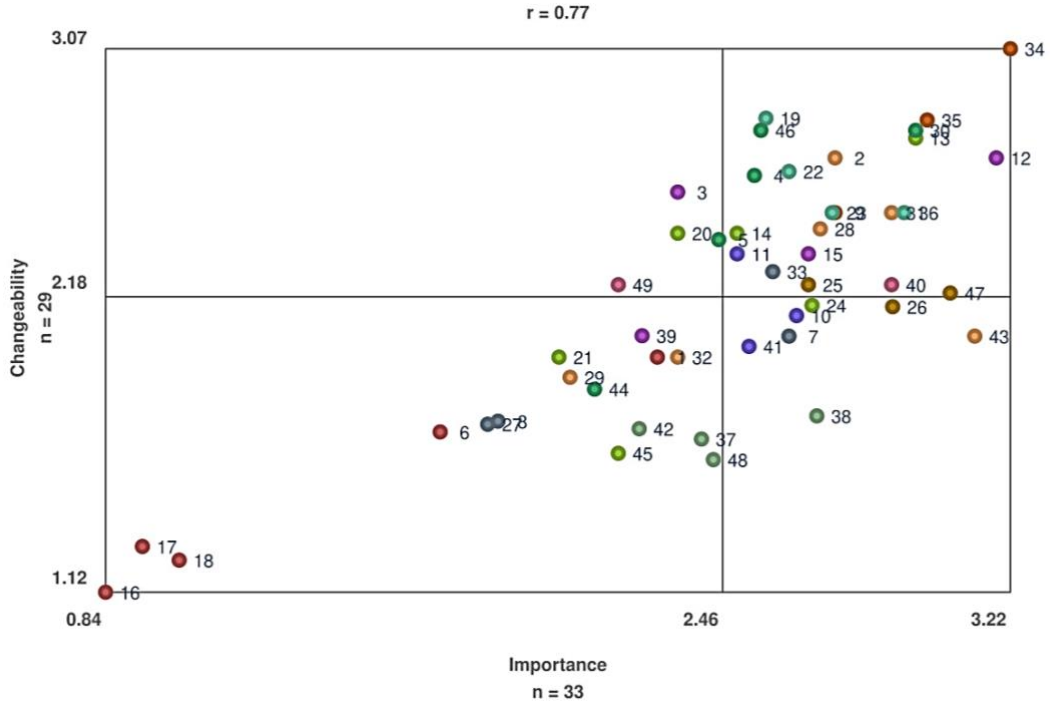

Figure 16. Go Zone display Importance vs. Changeability (i.e., it is possible to act on these factors to promote the adoption of MR-HIFU). Pearson's correlation coefficient (r) =0.77.

In contrast, none of the statements from clusters 'competitive treatments' and 'hospital costs' fell in the northeast quadrant. Statements located in the northeast quadrant are listed in the supplementary material (SM6).

4. Discussion

Evidence from the FURTHER trial is expected to be paramount to the adoption of MR-HIFU but is not enough to ensure successful adoption of this technology. The cluster map developed in our study elicited several individual experiences and offers a conceptual understanding of the factors that may influence the adoption of MR-HIFU in clinical practice. The low stress value (0.25) shows that participants sorted statements in a similar manner; however, the subgroups per country perceived the importance of these factors slightly differently.

In subgroup analysis per country, reimbursement is notably more important in Germany and the Netherlands compared to Finland, which might be explained by specific healthcare financing structures of these countries (Scheller-Kreinsen, Quentin, & Busse, 2011). For example, in Germany healthcare providers can negotiate supplementary bundled payment from statutory health insurances for innovative procedures (*Neue Untersuchungs- und Behandlungsmethoden*) (Simões Corrêa Galendi et al., 2022). In contrast, Finland has a system of cost-outlier payment (i.e., individual cases with exceptionally high costs are billed separately) and Finnish municipalities act as both payers and providers of healthcare (Scheller-Kreinsen et al., 2011). Moreover, in Germany and the Netherlands, the time lag between collection of data (e.g., resource use) and preparing the data for hospital reimbursement takes in average two years, while in Finland, this time-lag to data is less than one year (Scheller-Kreinsen et al., 2011).

In addition, divergences between countries could be explained by MR-HIFU being at different phases of implementation within the specific organizations or healthcare systems (Bak, Dobrow, Hodgson, & Whitton, 2011; Rogers, 1995). This could explain why in our results cluster 'clinical effectiveness' is perceived as the most important in all countries, except for Italy where cluster 'alignment of resources' is more important. A multiple case study on the adoption of intensity-modulated radiotherapy found that availability of resources is very important at a pre-implementation phase (i.e., when adopters are still forming an attitude about the innovation). In contrast, clinical evidence becomes more important in post-implementation phase (i.e., confirming the decision and continuing action) (Bak et al., 2011).

In healthcare markets, the adoption of technologies often follows a cyclical and dynamic process, more so for medical devices that are continuously being updated and enhanced with supplementary technology (Bak et al., 2011). There are several theories and frameworks describing the diffusion of innovations in healthcare (Clark, Dean, Bolton, & Beeson, 2020; Rogers, 1995). Based on literature review of theoretical and empirical studies, Greenhalgh et al. proposed a theoretical framework, the NASSS framework (Greenhalgh et al., 2017). The NASSS framework stands for Non-adoption, Abandonment, Spread, Scale-up and Sustainability of health and care technologies. According to NASSS framework, the probability of successful adoption depends on

the degree of complexity for seven domains: (i) the condition, (ii) the technology, (iii) the value proposition, (iv) the adopter system, (v) the healthcare organization and (vi) the wider system, and lastly (vii) the continuous embedding and adaptation over time (Greenhalgh et al., 2017; Greenhalgh et al., 2018).

The statements identified in our study generally fit the domains from the NASSS framework, even though the structure/categorization may deviate in some points (Greenhalgh, Robert, Macfarlane, Bate, & Kyriakidou, 2004; Greenhalgh et al., 2017). For example, the clusters 'alignment of resources' and 'logistics and workflow' reflect the complexity within the healthcare organization (domain v), and cluster 'physicians' attitude' reflect the complexity within the adopter system (domain iv). On the other hand, the statement 'bone metastases patients are often unfit for general anesthesia' (ID 45) highlights a complexity that could be intuitively placed within the condition domain. However, this statement was grouped in cluster 'physicians' attitude' because it was assumed to be an important part of the physicians' rationale. Hence, although the factors influencing the adoption of MR-HIFU echo previous findings, the relevance of each factor (and how they interact) is notably specific for the case studied (Greenhalgh et al., 2018).

According to our results, to promote adoption of MR-HIFU for pain palliation of bone metastases, clinical evidence from randomized clinical trials (statement 34) is seen as the utmost priority. This might result from the fact that 70% of our participants were involved in the FURTHER-trial. However, previous research has shown that the strength or quality of scientific evidence does not always have a large influence on the decision to adopt innovations in healthcare (Dreger et al., 2022; Urquhart et al., 2019). For many decision-makers, experiential knowledge can feel more relevant and applicable, and real-world data about the budgetary, operational, and patient impacts can have an equally high impact (Dreger et al., 2022; Urquhart et al., 2019).

Although cluster 'competitive treatments' was perceived as generally unimportant, it is noteworthy that 'radiotherapy as first-line treatment' was clustered separately. Radiotherapy is the current standard of care for patients with bone metastases (Rich et al., 2018), and its importance for the adoption of MR-HIFU is indubitable. However, the competitive advantage of radiotherapy seems difficult to overcome, largely due to the logistic advantages of radiotherapy and the already established referral workflow between care providers.

There were several advantages of GCM alongside a multicentric RCT. First, GCM enables to study the context in which the intervention will be applied, which is normally overlooked by the RCT design. About 30% of participants were not members of the FURTHER consortium, such as representatives from medical societies and regulatory bodies, who broadened the perspective of an otherwise highly specialized research group. Second, to a multicentric European RCT the online and asynchronous format was advantageous to engage participants who have busy schedules and are geographically dispersed (Cook & Bergeron, 2019). Third, GCM brainstorming

has been shown to be efficient in terms of time and financial costs compared to other qualitative research approaches such as interviews (Rising et al., 2019). Fourth, GCM offered a structured process that allowed engagement of different stakeholders while giving them equal voice and relevance (Trochim & Kane, 2005). The anonymous participation in the brainstorming task allowed participants to respond freely and may offset response behavior that can stem from hospital hierarchy (Trochim & Kane, 2005). Moreover, the involvement of stakeholders in the process itself creates commitment to adoption of the MR-HIFU (Trochim & Kane, 2005).

The online GCM format qualified as a reliable and practical solution for stakeholder engagement in face of the current travel restrictions imposed by the COVID pandemic. However, it should be acknowledged that the COVID pandemic could have influenced the perceived importance of some factors. For instance, the availability of anesthesiologist for MR-HIFU procedures was perceived as a very important factor. Because anesthesiologists were pulled from elective treatments to attend patients with COVID and were broadly unavailable for MR-HIFU treatments, the importance of this factor could have been overestimated.

Because MR-HIFU is in early phase of implementation in clinical practice and the novelty of the topic, the number of participants was representative to answer the research question. Although GCM studies can have larger sample sizes, the number of participants at each phase was appropriate to perform all GCM analyses (Trochim & Kane, 2005). The overall participation rate was similar to the average participation of online-based qualitative studies, which according to a systematic review is 44.1% (Wu, Beaton, Smith, & Hagen, 2010). One important limitation of the present GCM study was low patient representation. The patient group consists of older patients with advanced cancer, who have multimorbidity, limited mobility and limited life expectancy. The online format was thought to be appropriate because it would abstain from in person interaction (e.g., as needed for focus groups). However, patient recruitment for the FURTHER trial stopped for two years during the COVID pandemic. As a result, only six patients were invited to participate or to appoint a representative but five declined mainly due to language barrier. Future studies that intend to apply GCM methodology in the context of a multinational trial should consider engaging patients in their own language.

5. Conclusions

In conclusion, GCM offered a structured process that promoted engagement of different stakeholders alongside the FURTHER-trial. The resulting concept maps shed light on how the participants discern the interrelationships and relevance of factors that may influence the adoption of MR-HIFU in clinical practice in Europe. Although these are likely to change as the technology evolves and the implementation process continues, the present GCM study was able

to construct a common understanding among participants. The findings of this GCM study can be used as basis to develop strategies and recommendations on how to support the adoption of MR-HIFU in European oncologic care.

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Chapter VII

Health economics of MR-HIFU for painful bone metastases: advances and challenges that lie ahead

MR-HIFU holds the promise of providing equivalent pain relief, but faster pain palliation to patients with advanced cancer and painful bone metastases. This cumulative dissertation has the objective of providing early health economic evidence to support the adoption of MR-HIFU in clinical practice. The three dissertation subprojects presented in this cumulative dissertation aimed to determine the costs of the MR-HIFU (subproject I), the cost-effectiveness of MR-HIFU compared to EBRT (subproject II), and lastly, contextual factors influencing the adoption of MR-HIFU for treatment of bone metastases (subproject III).

1. Methodological strengths and limitations

1.1. Challenges and limitations

Methodological challenges and limitations to this cumulative dissertation must be acknowledged. The main methodological limitation is related to the uncertainty in results, especially in the cost calculation in subproject I, which was based on small case series, and in the cost-effectiveness analysis in subproject II, which was based mainly on literature data.

Because the sample size for the cost calculation (subproject I) was small, it was not possible to determine the impact of clinical variables, such as tumor volume or type of bone tumor, on the treatment duration and overall costs. Moreover, because time measurements were obtained retrospectively (2018-2019) and prospectively (2020-2021), it was not possible to demonstrate the impact of learning curve on costs (Simões Corrêa Galendi, Yeo, Simic, et al., 2022). Retrospective time measurements are subject to recall bias, while interference from the observer in the normal care practices can bias prospective time measurements (Maussen & Hoozée, 2022). Hence, the trend of reducing MRI occupancy and sonication times might be circumstantial or biased by different methods for measuring time (Simões Corrêa Galendi, Yeo, Simic, et al., 2022). To solve the remaining uncertainties regarding learning curve and cost trends per tumor subgroup, a larger number of observations and time measurements is needed.

The methodological limitations of the early economic modeling (subproject II) were mainly related to the quality of the primary data applied to the model. Due to a lack of a direct clinical comparison between the treatment alternatives and short follow-up of MR-HIFU studies, the model had to be based on different clinical studies and several assumptions. As a result, there

was considerable uncertainty in the model results. In addition, the choice of comparator reflects the EBRT practices in Germany (i.e., mainly multi-fraction EBRT), which may limit the generalizability of the results to other settings where single-fraction is preferred (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022).

Lastly, the most important limitation of the GCM study (subproject III) was low patient representation as only one patient participated in the study.

1.2. Methodological strengths

Even under high uncertainty, health economic evidence can be valuable if the analyses are transparently reported, and the source of uncertainty is thoroughly explored. Transparency in reporting and exploration of uncertainty are the two main methodological strengths of this cumulative dissertation.

Transparency in reporting is important because it enables reproducibility to other settings. In subproject I, the reporting of the cost calculation using the stepwise approach is in line with consensus statements from TDABC working groups (Etges, Polanczyk, & Urman, 2020). Moreover, the European care pathway was based on intricate detail from four European countries, which will serve as cost allocation framework for future cost comparisons. In subproject II, extensive validation efforts were undertaken, which enables the reproducibility of the model once additional evidence is available. Validation efforts were transparently reported according to the 'Assessment of the Validation Status of Health Economic decision models' checklist, increasing reliability of the model assumptions.

In the cost calculation (subproject I) and in the cost-effectiveness analyses (subproject II), uncertainty was thoroughly explored by scenario analyses and deterministic, structural, and probabilistic analyses. In addition, the VOI analysis based on the early economic modeling (subproject II) stands out. An explicit representation of uncertainty is useful in determining whether funding for conducting further research would be economically worthwhile and informing research prioritization. Although most early economic modeling studies conclude that further research is necessary, VOI analyses are still underused (Grutters et al., 2019; Love-Koh, 2020). In a systematic review of cost-effectiveness analyses of treatments for bone metastases, none of the 24 included studies conducted a VOI analysis (Andronis, Goranitis, Bayliss, & Duarte, 2018).

In addition, a further strength of this cumulative dissertation was the combination of quantitative and mixed-methods research. Although evidence on cost and cost-effectiveness are extremely important, the participatory research reported in subproject III offers a broader view of the barriers and drivers influencing the adoption of MR-HIFU in clinical practice. GCM as a participatory research method offered a structured process that promoted engagement of different stakeholders alongside the FURTHER project (Trochim & Kane, 1989). The anonymous

participation in the brainstorming task allowed participants to express themselves freely, equalizing power differentials that can arise from hospital hierarchy (Trochim & Kane, 2005).

2. Relation to the current state of research

2.1. Previous applications of TDABC

TDABC is a micro costing methodology linked to the concept of value-based healthcare. This concept claims that 'value' for patients should be the overarching goal of healthcare delivery and defines 'value' as the health outcomes achieved per cost unit spent over the entire care process (Porter, 2010). Health outcomes are an important part of the equation, but costs remain largely unmeasured and misunderstood. Thus, the TDABC approach was proposed to fill this gap. TDABC serves the value-based healthcare agenda well, because it enables care providers to control costs by improving patient care pathways (Keel, Savage, Rafiq, & Mazzocato, 2017). To date, TDABC has been most often applied to hospital services. A systematic review identified that 90% of studies applying TDABC before 2018 were conducted in the inpatient setting, mostly in surgical wards (68% of 25 studies included) (Keel et al., 2017).

Applications of TDABC to radiotherapy are increasing. The European Society for Radiotherapy and Oncology (ESTRO) proposed TDABC as standard approach for enabling EBRT provision in Europe (Defourny et al., 2019). For a hypothetical European country, single-fraction EBRT for pain palliation on bone metastases costs €1,275 from the payer perspective (Defourny et al., 2019). The application of TDABC for EBRT in a large scale provided a two-fold advantage: not only does it allow tracking costs more accurately at the activity level, but it also provides insight into resource utilization in relation to the available capacity in Europe. For instance, while 94% of the clinical personnel capacity in Europe is in use, other resources are relatively abundant (e.g., only 15% of the dosimetry equipment are being used) (Defourny et al., 2019).

It is worth mentioning that the application of TDABC is possibly underestimated in the literature, since these studies do not always use a common nomenclature (Etges, Ruschel, Polanczyk, & Urman, 2020). For example, Knuttel et al. estimated the costs associated with provision of MR-HIFU for patients with minimally invasive breast cancer (Knuttel et al., 2017). Although the authors applied a similar stepwise approach, based on the development of a care pathway and time measurements, the methodology is broadly described as early health technology assessment (Knuttel et al., 2017). Recently published consensus statements from TDABC working groups, which were used as basis for subproject I, are expected to stimulate standard reporting for TDABC studies, increasing transparency and reliability of cost calculations (Etges, Polanczyk, et al., 2020).

The TDABC study developed in subproject I is the first micro costing study of MR-HIFU for bone metastases (Simões Corrêa Galendi, Yeo, Simic, et al., 2022). Because of the increasing

relevance of TDABC to the value-based healthcare agenda, this was the most appropriate approach to calculate the costs of MR-HIFU. The European care pathway developed in subproject I can be used to collect data on resource use within the FURTHER RCT and provides the opportunity of benchmarking the provision of MR-HIFU Europe. Moreover, it provided an accurate cost calculation from the perspective of the UHC, which could be used to assess the cost-effectiveness of MR-HIFU for bone metastases.

2.2. Cost-effectiveness of treatments for bone metastases

Cost-effectiveness analyses of treatments for patients with bone metastases face one common challenge related to the heterogeneity within this patient population. Depending on the primary tumor type, patients have considerably different life expectancies. Due to this heterogeneity, many cost-effectiveness analyses focused on one type of tumor. In a systematic review of cost-effectiveness analyses, 17 out of 24 studies assessed only one tumor type, the most common being prostate, breast, lung or renal (Andronis et al., 2018). In this review, only five studies conducted subgroup analysis according to various types of tumors, which was found to be an insightful aspect in subproject II.

The cost-effectiveness of EBRT has been assessed in previous studies, mostly to compare single-fraction versus multi-fraction (Andronis et al., 2018). Both fractionation schemes have equivalent effectiveness, but single-fraction is considerably less costly. As a result, single-fraction is considered cost effective for patients with bone metastases. This finding was confirmed in different settings, including an RCT-based cost-utility analysis from the Netherlands (van den Hout et al., 2003), and model-based cost-effectiveness analyses from the U.S., New Zealand and France (Cai, Nickman, & Gaffney, 2013; Collinson, Kvizhinadze, Nair, McLeod, & Blakely, 2016; Kim, Rajagopalan, Beriwal, Huq, & Smith, 2015; Konski, 2004; Le Fèvre et al., 2019).

In addition, another innovative intervention for bone metastases has been recently investigated. Chang et al. assessed the cost-effectiveness of percutaneous image-guided cryoablation compared to radiotherapy for uncomplicated bone metastases (Chang, Shaverdian, Capiro, Steinberg, & Raldow, 2020). Chang et al. concluded that cryoablation might be cost effective for the U.S. as retreatment strategy after failed EBRT (ICERs of $85,000 to $96,000/QALY). However, cryoablation was not cost effective as a first-line treatment because it costs $9,000-10,000 more than EBRT only and generates no additional benefits, resulting in ICERs up to $500,000/ QALY (Chang et al., 2020). Although there is no direct compassion of cryoablation and MR-HIFU, these findings indicate that cryoablation has probably low relevance as competitive treatment to MR-HIFU.

To date, the only other health economic evaluation of MR-HIFU for painful bone metastases dates 2021. Bucknor et al. compared MR-HIFU to medication only from the payer perspective in the US setting (Bucknor, Chan, Matuoka, Curl, & Kahn, 2020). This model showed

that MR-HIFU resulted in both incremental costs ($11,863) and QALYs (0.22), compared to medication only. The resulting ICER was $54,160 /QALY (Bucknor et al., 2020). In subproject II, the ICER was much lower, about €19,000 /QALY (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). However, the comparability of the results is limited due to several methodological differences. Table 9 contrasts the main methodological differences between the studies from Bucknor et al. and subproject II (Simões Corrêa Galendi et al., 2022).

Table 9. Methodological differences between Bucknor et al., 2020, and subproject II

	Bucknor et al., 2020	**Simões Corrêa Galendi et al., 2022**
Setting	U.S.	Germany
Patient Population	Patients with refractory pain after previous EBRT	Patients with painful bone metastases, with or without previous EBRT
Intervention	MR-HIFU as second line treatment (could be repeated 3 times)	MR-HIFU could be offered once as first-line or second line treatment after EBRT
Comparator	Medication Only (opioids)	EBRT
Outcome	$/QALY	€/QALY and €/month with pain response
Model type	Markov model	Patient-level simulation model
Time horizon	Two years	Lifetime
Adverse events from treatments	Not considered	Considered in benefits, but not in costs
Pathological fracture	Not considered	Modeled as an event
Subgroup analyses	Not conducted	Subgroup analyses per cancer type
VOI analyses	Not conducted	Calculation of EVPI and EVPPI

Abbreviations: US: United States of America, MR-HIFU: Magnetic resonance-guided High-Intensity Focused Ultrasound, VOI: value of information, EVPI: expected value of perfect information, EVPPI: expected value of partial perfect information.

However, both analyses concluded that MR-HIFU is potentially cost effective for patients with bone metastases. By assuming a WTP threshold of $100.000 /QALY, Bucknor et al. conclude that there is 67% probability that MR-HIFU is cost effective in the U.S. for patients with refractory bone pain, compared to medication only (Bucknor et al., 2020). Whereas in subproject II, we concluded that, at a WTP of € 40,000/QALY, there is a 64% probability that the MR-HIFU-based

strategy is cost effective when compared to EBRT (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). Thus, in these two different settings, MR-HIFU has shown potential added value to patients with bone metastases.

2.3. Factors influencing the adoption of healthcare technologies

The adoption of technologies should be underpinned by the evidence of value (i.e., from effectiveness trials and cost-effectiveness analyses). However, contextual factors have proven to play an important role in the adoption of technologies (Urquhart et al., 2019). In subproject III, the participants explored 12 clusters of factors that might impact the adoption of MR-HIFU in Europe (Simões Corrêa Galendi et al., 2023), which are summarized hereafter in order of importance:

a) 'Clinical effectiveness': evidence on effectiveness from RCTs was perceived as the most important factor to the adoption of MR-HIFU. The FURTHER RCT is expected to fill this gap.
b) 'Radiotherapy as first-line therapy': EBRT is an effective treatment for bone metastases, and the competitive advantage of EBRT, mainly due to established referral logistics, is difficult to overcome.
c) 'Patients' preferences': characteristics of the MR-HIFU technology might be appealing to the patient, especially because MR-HIFU is non-invasive, and can be performed in the outpatient setting.
d) 'Alignment of resources': To perform a MR-HIFU treatment, it is challenging to coordinate the availability of radiology and anesthesiology teams, and the vacancy of MR room. Frequency of time slots at the MRI dedicated for HIFU would be a measure to help scale adoption of MR-HIFU.
e) 'Aggregating knowledge & improving awareness': The role of MR-HIFU in the broader clinical practice is still unclear. The inclusion of MR-HIFU in clinical guidelines would stimulate the adoption of MR-HIFU.
f) 'Reimbursement': appropriate reimbursement is a key aspect to the adoption of MR-HIFU. Notably, reimbursement was considered a very important factor in Germany and in the Netherlands, but not in Finland. These differences are justified by different healthcare systems and their financing structures.
g) 'Cost-effectiveness': cost-effectiveness analyses help establish the value for money of MR-HIFU in comparison to EBRT. Cost-effectiveness was explored in subproject II (Chapter V).
h) 'Logistics and workflow': patients with bone metastases are heterogeneous, and therefore, the range of referring specialists is wide. Creating standard workflows

for referrals, both within and between hospitals, would support the adoption of MR-HIFU.

i) 'Physicians' attitudes': physicians might be resistant to adopting MR-HIFU, because they lack time to get familiar with the innovation and to overcome the logistical difficulties. Besides, they might have an intrinsic resistance to change.
j) 'Hospital costs': MR-HIFU is perceived as resource- and cost-intensive. Hospital costs were thoroughly explored in subproject I (Chapter IV).
k) 'Competitive treatments': competitive treatments other than EBRT were considered widely unimportant to the adoption of MR-HIFU. For instance, cryoablation is more invasive, and was not cost effective as a primary treatment in the United States (Chang et al., 2020).

In subproject III, the evidence on effectiveness was considered the most important factor to the adoption of MR-HIFU, probably because 70% of participants are involved in the FURTHER project (Simões Corrêa Galendi et al., 2023). However, the automatic transfer of evidence to practice is not the rule, as has been demonstrated in several case studies in oncology (Urquhart et al., 2019). An akin on-topic example of this phenomenon is the choice of EBRT fractionation scheme for pain palliation of bone metastases.

Single-fraction promotes equivalent pain relief as multi-fraction EBRT, as has been demonstrated in meta-analyses including 25 RCTs and 5,617 patients with painful uncomplicated bone metastases (Rich et al., 2018; Sze, Shelley, Held, & Mason, 2004). In addition, there is evidence that single-fraction is cost effective when compared to multi-fraction EBRT, mainly due to lower costs (Cai et al., 2013; Collinson et al., 2016; Kim et al., 2015; Konski, 2004; Le Fèvre et al., 2019; van den Hout et al., 2003). Based on this body of evidence, most guidelines recommend single-fraction due to its cost-effectiveness and the convenience for patients and caregivers (Ganesh et al., 2017; van der Velden et al., 2022).

However, the adoption of single-fraction EBRT is strongly impacted by reimbursement modalities and healthcare financing. Countries with predominant budget and case payment modalities, such as the Netherlands and U.K. reported highest proportions of single-fraction use. In contrast, countries with predominant fee-for-service reimbursement modalities (payment per fraction), such as Switzerland, Austria and Germany prefer multi-fraction schemes (Ganesh et al., 2017; Lievens, Kesteloot, Rijnders, Kutcher, & Van den Bogaert, 2000). Consequently, EBRT practices are extremely heterogeneous across countries. In addition, according to a multiple case study design from Canada, key factors that influenced the extent of the adoption of innovations within the EBRT practices are (i) leadership, (ii) training, expertise, and standardization, (iii) collaboration, (iv) resources and (v) resistance to change (Bak, Dobrow, Hodgson, & Whitton, 2011).

Analogous to the adoption of EBRT and other complex technologies, the adoption of MR-HIFU will be influenced by several contextual factors (Foley et al., 2013). These contextual factors should not be overlooked, as they might lead to later abandonment or might endanger the spread, scale-up and sustainability of a technology in healthcare (Greenhalgh et al., 2017). The findings of subproject III can be used by the FURTHER consortium as basis to develop strategies and recommendations on how to support the adoption of MR-HIFU in Europe for the treatment of bone metastases.

3. Implications for research and practice

3.1. Research prioritization

To enhance early access to innovative health technologies, reimbursement decisions are increasingly made when the evidence base is still immature (Ijzerman & Steuten, 2011). However, when decisions are made under uncertainty, the consequences might be costly for the healthcare system (e.g., listing a procedure that is later found not to be cost-effective) and suboptimal for the patient (e.g., delaying adoption of a treatment that improves patients' outcomes) (Fenwick et al., 2020). Intuitively, decision uncertainty can be reduced by collecting more evidence, but additional research may not be worthwhile if the direct research costs are higher than the expected 'payback' (value) from research (Fenwick et al., 2020).

The VOI analyses (subproject II) investigated if additional evidence has value for the decision on adding MR-HIFU to the treatment of bone metastases (in comparison with having EBRT only). The results (summarized in figure 17) indicate that collecting additional evidence on MR-HIFU is worthwhile to optimize patients' outcomes from the perspective of the German SHI (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022).

Extrapolated to the German population over a period of five years, the value of additional evidence was €178 Mio, this is the maximum amount that should be invested into additional research to reduce uncertainty for this decision (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). Moreover, five parameters contribute the most to decision uncertainty: costs of MR-HIFU, fracture rate associated with MR-HIFU, utilities, EBRT practices (i.e., whether single-fraction or multi-fraction is the comparator), and lastly, effectiveness of MR-HIFU (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). Therefore, collection of additional evidence on these parameters should be prioritized.

To provide high-quality evidence on the effectiveness of MR-HIFU the RCT design is indubitably the most appropriate, and the FURTHER RCT is expected to fill this gap (Napoli et al., 2023; Slotman et al., 2022). However, collection of real-world data on MR-HIFU effectiveness (e.g., through a registry) could be useful to study patients that are not eligible for randomization, those

who either have a strong preference for MR-HIFU or whose lesion or clinical condition is extremely favorable to one of treatment alternatives.

In addition, real-world data could be applicable for reducing uncertainty regarding (i) costs of MR-HIFU procedure and (ii) fracture rates following MR-HIFU treatments:

(i) Costs of MR-HIFU procedure in the context of an RCT might be overestimated due to protocol-related cost components, such as supernumerary personnel to collect data or to supervise the protocol adherence (Koopmanschap, Touw, & Rutten, 2001). Although it is opportune to collect cost data alongside RCTs, it can be challenging to depict these protocol-related costs independently (Koopmanschap et al., 2001).

(ii) Fractures following MR-HIFU treatment, although extremely costly events, are rare. For instance, the fracture rate in the placebo-controlled RCT of MR-HIFU was 1.8% in three months follow-up (Hurwitz et al., 2014). This might result from strict inclusion criteria in RCTs, such as those applied to the FURTHER RCT, in which patients at higher risk for fracture will be excluded (Slotman et al., 2022). Thus, observational data might be helpful to complement the evidence generated in RCTs and the impact of fractures in the cost-effectiveness of MR-HIFU.

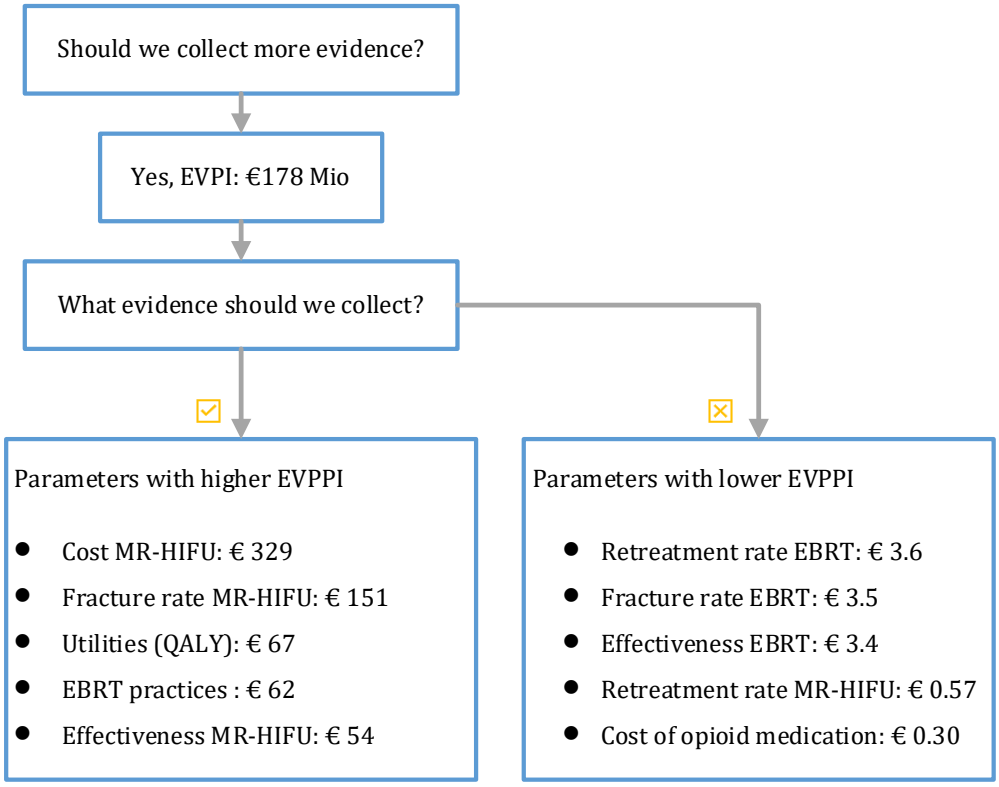

Figure 17. Summary of value of information analysis results, adapted from Simões Corrêa Galendi, Yeo, Grüll, et al., 2022. Abbreviations: EVPI: Expected value of perfect information. Expected value of partial perfect information. MR-HIFU: Magnetic resonance-guided High-Intensity Focused Ultrasound, EBRT: External Beam Radiation Therapy.

3.2. Cost-effectiveness analysis using FURTHER RCT data

Cost-effectiveness and cost-utility are secondary endpoints of the FURTHER RCT. Based on the European care pathway and cost calculation for Germany (subproject I) and the early economic modeling study (subproject II), it was possible to anticipate challenges to a future trial-based cost-effectiveness analysis.

Multinational trials such as the FURTHER RCT offer the opportunity to optimize patient accrual with relative confidence that the health effects will be the same across countries (Koopmanschap et al., 2001; Oppong, Jowett, & Roberts, 2015; Reed et al., 2005). However, collecting and aggregating economic data alongside multinational trials poses many challenges due to the incomparability of medical resource consumption and costs between countries (Koopmanschap et al., 2001; Oppong et al., 2015).

In the context of the FURTHER RCT, the incomparability of medical resource consumption and costs might stem from three main aspects: (i) different patterns of medical practice, (ii) influence of patient characteristics and epidemiology, and (iii) impact of absolute and relative prices of medical services (Koopmanschap et al., 2001).

(i) Patterns of medical practice might be the most important variable determining the incomparability between countries within the FURTHER RCT, because divergences can be found both in the intervention arm (MR-HIFU) and the control arm (EBRT). First, for MR-HIFU treatments, there is high variability between countries regarding the anesthesia practice (i.e., general anesthesia vs. sedation). These variations in anesthesiologic approaches have potential impact on costs, as discussed in subproject I. Moreover, because general anesthesia ultimately leads to longer hospital time, it might impact patients' preferences (and QALYs) negatively. Hence, variations in anesthesia practices might lead to different conclusions regarding the total costs and the cost-effectiveness of MR-HIFU in different countries.

Second, the EBRT practices are extremely heterogeneous across countries. The EBRT practices might be especially impactful for the cost-effectiveness of MR-HIFU (when compared to EBRT) in countries with fee-for-service reimbursement. In subproject II, we determined the cost of single-fraction as €1,486 in comparison to €3,610 for multi-fraction (considering the mix-case of in- and out-patient) (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). Sensitivity analyses concluded that a (hypothetical) increased use of single-fraction decreases the comparator's costs, thus resulting in higher ICERs – in other words, MR-HIFU-based strategy is less likely cost effective.

(ii) Patient characteristics such as severity of illness can impact cost-effectiveness analysis in the context of a multinational trial, if patient characteristics are distributed unequally between countries (Koopmanschap et al., 2001). For the cost-effectiveness of MR-HIFU, tumor type is a relevant characteristic. In subproject II, the MR-HIFU-based strategy was slightly more cost effective for patients with lung cancer, who have a much poorer life expectancy than breast

and prostate cancer (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). However, adequate randomization and the strict inclusion criteria might be enough to avoid that patient characteristics are distributed unequally between countries (Koopmanschap et al., 2001).

(iii) Absolute and relative prices can also lead to the incomparability between countries. Even within Europe, healthcare prices differ considerably (Koopmanschap et al., 2001). Because healthcare is a labor-intensive sector, these differences are often related to wage levels (Koopmanschap et al., 2001). The case of MR-HIFU is no exception because wages represent a high share of total costs. Costs with personnel represents 32% (€1,621) of total costs of MR-HIFU form the hospital perspective in Germany and specifically medical personnel (i.e., interventional radiologist and the anesthesiologist) represented 56% of personnel costs (Simões Corrêa Galendi, Yeo, Simic, et al., 2022).

Considering the incomparability of medical resource consumption and costs between countries, a fully split instead of a fully pooled cost-effectiveness analysis would be recommended once trial data is available. A fully split cost-effectiveness consists of calculating one ICER per country. Although it is feasible to pool cost data for the RCT and calculate one ICER for all countries (i.e., so called fully pooled cost-effectiveness analysis), aggregating resource consumption and costs from different countries will not give valid results and may not address national health policy issues properly (Koopmanschap et al., 2001; Oppong et al., 2015; Reed et al., 2005).

In addition, using country-level data both on resource use and costs would be preferable. To minimize the impact of different patterns of medical practice, a structured and transparent cost collection is the preferred approach (Koopmanschap et al., 2001). The cost allocation framework (subproject I) was developed based on clinical practices from all countries and thus fits this purpose.

3.3. Implications for hospital management and technology developers

First and foremost, the early evidence that MR-HIFU is potentially cost effective for patients with bone metastases is useful to manufacturers, indicating that further investments in product research and development would be worthwhile. Moreover, for the hospital it is an indication that investments with installation and personnel training are unlikely to lead to sunk costs (Grutters et al., 2019).

With regard to Germany, it is possible to conclude that the current gDRG lump-sum is not cost covering for the hospital. Currently, the cost of MR-HIFU from the hospital perspective amounts to €5,147 (Simões Corrêa Galendi, Yeo, Simic, et al., 2022). In contrast, the gDRG yields a reimbursement of €3,372, relative to the gDRG codes C40.1 and C40.2, the OPS code for MR-HIFU - 5-789.7 and one overnight stay (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). Although a readjustment of the gDRG would mitigate losses from the hospital perspective, this would implicate in a lower cost-effectiveness of MR-HIFU in relation to the EBRT. Considering a cost-

covering lump-sum for MR-HIFU (i.e., €5,147), the resulting ICER would be €77,650 /QALY gained, which is four times higher than the base case (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022).

An alternative measure to increase competitive advantage of MR-HIFU in relation to EBRT would be to act on hospital costs. Technology developers and hospital management could collaborate to optimize the patient trajectory, making the care process more agile, which would reduce time occupancy of the MRI room and reduce costs (Simões Corrêa Galendi, Yeo, Simic, et al., 2022). In addition, this measure would also improve logistics and patient experience, and address the physicians' perception that MR-HIFU is too lengthy, which are contextual factors identified as relevant to the adoption of MR-HIFU (Simões Corrêa Galendi et al., 2023).

3.4. Implications for clinical practice

Two main implications for clinical practice can be drawn. First, the finding that MR-HIFU was slightly more cost effective for patients with metastatic lung cancer can inform patient selection for MR-HIFU treatment. It was previously hypothesized that patients with breast and prostate cancer would benefit more from MR-HIFU because they have longer life expectancy (Huisman et al., 2015). However, when compared to EBRT, the greater added benefit of MR-HIFU lies in the fact that it provides more rapid pain palliation (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). Hence, patients with shorter life expectancy, such as lung cancer patients, benefit equally and the value for money in this patient population is the same.

Second, when interpreting the health economic evidence in light of the broader clinical practice, the relevance of pathological fractures should be highlighted. Although the primary goal of MR-HIFU is pain palliation, pathologic fracture is an important clinical outcome, and a costly one. Consequently, bone fractures proved to be critical to the cost-effectiveness of MR-HIFU (Simões Corrêa Galendi, Yeo, Grüll, et al., 2022). Therefore, practitioners should ensure that MR-HIFU patients are adequately prescribed the co-strategies that have proven to reduce the risk of fracture, such as BTAs (Jakob et al., 2022; Machado, Cruz, Tannus, & Fonseca, 2009; Menshawy et al., 2018).

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Conclusion

MR-HIFU is a promising treatment alternative to pain palliation of patients with painful bone metastases. The FURTHER project aims to evaluate the effectiveness of MR-HIFU compared to the EBRT in an RCT, but early health economic evidence was needed to support the adoption of MR-HIFU in clinical practice. The three dissertation subprojects presented in this cumulative dissertation aimed to determine the costs of the MR-HIFU, the cost-effectiveness of MR-HIFU compared to EBRT, and lastly, contextual factors influencing the adoption of MR-HIFU for treatment of bone metastases.

Considering the current reimbursement lump-sum, MR-HIFU is potentially cost effective for patients with bone metastases from the perspective of the German SHI. On the other hand, the reimbursement for an MR-HIFU procedure is currently not cost covering for the hospital in Germany. Improvements to the care pathway could reduce costs of MR-HIFU, which would be beneficial to the hospitals and subsequently impact the cost-effectiveness in relation to EBRT from a payer perspective.

Further research is worthwhile to better inform the decision whether to adopt MR-HIFU as a treatment alternative. Although the micro costing study and the cost-effectiveness analysis presented in this cumulative dissertation focused on the German context, the findings have several implications for future research, especially recommendations for a future cost-effectiveness analysis using data from the FURTHER project. In addition, the cost allocation framework was developed considering practices from Germany, Netherlands, Italy, and Finland and can support data collection on resource consumption in the FURTHER RCT.

Finally, to ensure successful adoption of MR-HIFU in Europe, several contextual factors should be addressed jointly, such as physicians' attitudes, hospital logistics and patients' preferences. Beyond the direct effects of MR-HIFU and its comparator, the health economic findings presented in this cumulative dissertation should be interpreted considering the healthcare context and without losing sight of the broader clinical practice.

Appendix

Supplementary material to chapter IV

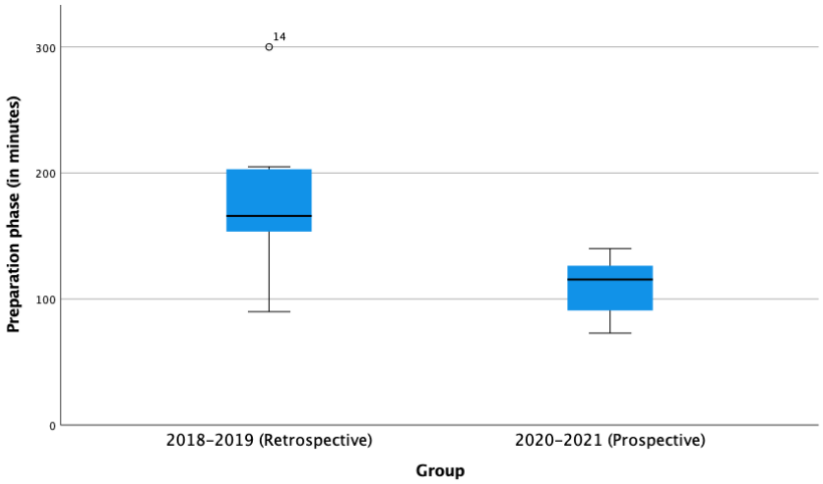
Contents

Table 1A Characteristics of centers and participants on the development of the care pathway

	Center 1	**Center 2**	**Center 3**	**Center 4**	**Center 5**
Description	University Hospital of Cologne, Cologne	Stichting Isala Klinieken, Zwolle	University Medical Center, Utrecht	Turku University Central Hospital, Turku	Istitituto Ortopedico Rizzoli (IOR), Bologna
Country	Germany	The Netherlands	The Netherlands	Finland	Italy
Characteristic	University Hospital	Private Hospital	University Hospital	University Hospital	University Hospital
Participants on the development of the care pathway	One interventional radiologist, one clinical researcher, two technicians	One clinical researcher, one interventional radiologist, one technician, one seditionist, one nurse	One clinical researcher, one interventional radiologist, one technician, one seditionist, one nurse	Two interventional radiologists, one physicist, three technicians, one clinical oncologist, one anesthetist	One interventional radiologist, one nurse, one technician, one anesthesiologist and one orthopedic oncologist

Table 2A Expected heterogeneity among centers according to participants

	Center 1	**Center 2**	**Center 3**	**Center 4**	**Center 5**
Anesthesia	General anesthesia	Conscious sedation or General anesthesia (10%)	Conscious sedation	Conscious sedation or General anesthesia	Spinal Anesthesia (90%) and general anesthesia (10%)
Composition of the anesthesia team	Anesthesiologist and assistant	Anesthesiologist and assistant if general anesthesia; sedationist if conscious sedation	Sedationist	Anesthesiologist and assistant if general anesthesia; sedationist if conscious sedation	Anesthesiologist and assistant
Need for overnight stay	Always	Rarely	Rarely	Uncommon	Frequent



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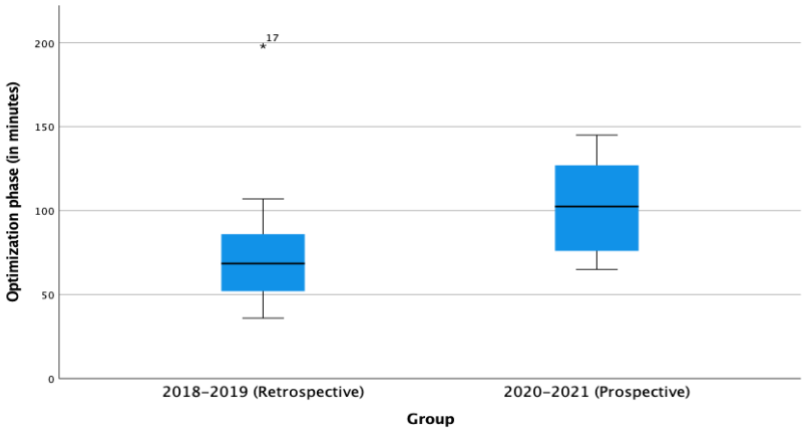

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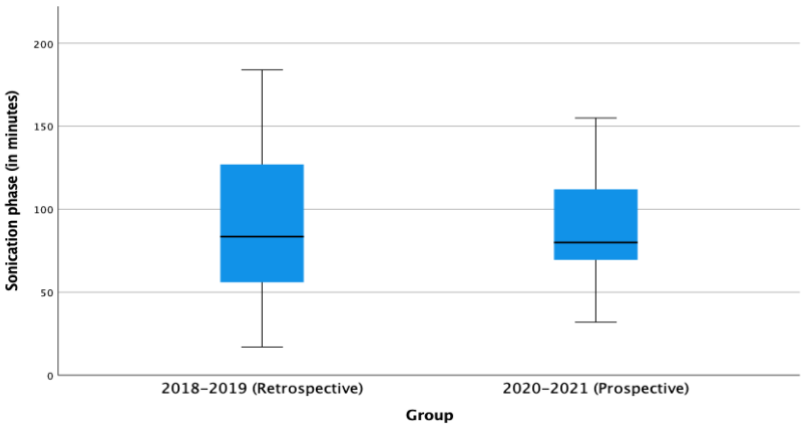

C

Figure 1A Chrono analysis; duration of each module of the care pathway (macro level) comparing patients treated between 2018-2019 (data collected retrospectively) and between 2020-2021 (data collected prospectively).

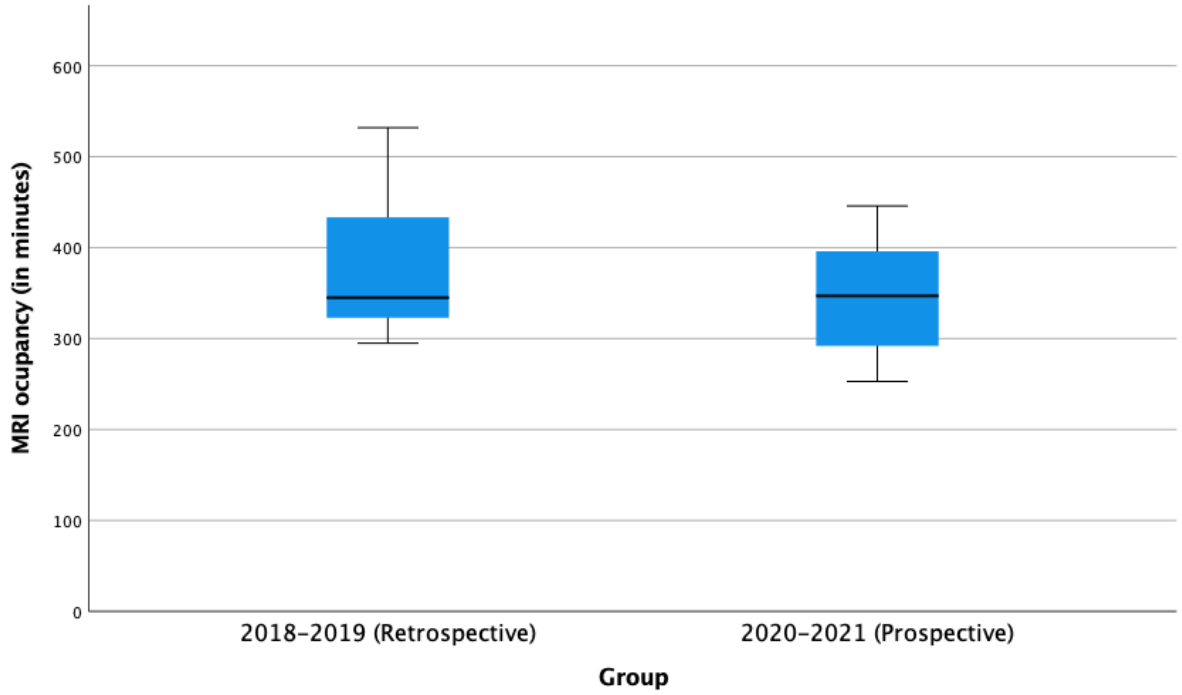

Figure 2A Chrono analysis demonstrating the duration of MRI occupancy comparing patients treated between 2018-2019 (data collected retrospectively) and between 2020-2021 (data collected prospectively).

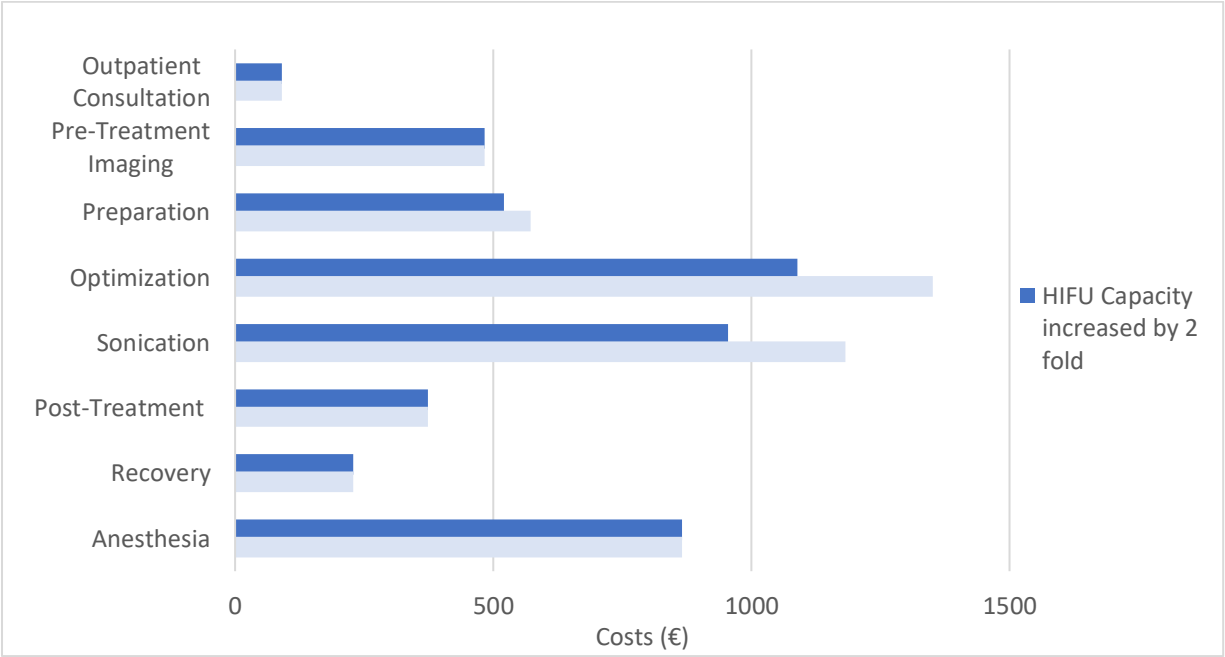

Figure 3A Cost per module of the care pathway in the base case and considering a higher capacity of the HIFU

Appendix

Supplementary material to chapter V

Contents

SM 1 Cost calculation of MR-HIFU and EBRT treatments based on diagnosis and procedure codes

Inpatient costs of EBRT were based on a 14-day length of stay (including one planning CT and consultation for informed consent (day one); irradiation simulation (day two), and irradiation on days nine to 14) (Table S1). Outpatient costs were calculated considering the treatment dose of 20Gy x5 and 8Gy x1 including the relevant surcharges (Table S2). Inpatient costs calculated for MR-HIFU are shown on table S3.

Table S1. Radiotherapy – outpatient codes and respective flat rates

	EbM code	Description	Flat rate
A	25211	Consultation flat rate for malignant disease or space-occupying processes of the central nervous system (once per treatment)	117,28 €
B	25214	Consultation flat rate after radiotherapy treatment in accordance with the guidelines under the Ordinance on Protection against Damage Caused by Ionizing Radiation (Radiation Protection Ordinance) (once per treatment)	28,95 €
C	25342	Computer-assisted radiation planning for percutaneous irradiation with individual dose planning for irregular fields with individual blocks, multi-lamella collimator, non-coplanar fields and/or 3-D planning	473,18 €
D	25343	Surcharge for fee schedule position 25342 for computer-assisted high-precision radiation planning (IMRT and/or fractionated stereotaxy) (per radiation series)	574,69 €
E	34360	CT-guided examination of organ sections for radiation planning in teletherapy or brachytherapy	39,88 €
F	01600	Medical report on the result of a patient examination	6,2 €
G	01601	Physician's letter in form of individual written information from the physician to another physician about the patient's health or medical condition	12,17 €
H	01602	Multiple Manufactures (e.g., copy) of a report or letter to the primary care physician	1,35 €
I	40110	Flat-rate charge for sending or transporting a letter and/or written documents	0,81 €
J	25321	Radiation with a linear accelerator for malignant diseases or space-occupying processes of the central nervous system	86,86 €
K	25324	Surcharge for more than 1 target volume (malignant disease) [up to 2 each]	23,88 €
L	25325	Surcharge for high-precision technology for malignant diseases	24,79 €
M	25327	Surcharge for fee schedule position 25321 for irradiation using high-precision technology in combination with image-guided setting (IGRT)	47,32 €
N	25328	Surcharge for fee schedule position 25321 if the individual dose is exceeded ≥ 2.5Gy	48,44 €
Total cost per patient:			
A+B+C+D+E+F+G+H+I+5x(J+K+L+M+N)		Cost per patient, 5x 4Gy	2.410,96 €
A+B+C+D+F+G+H+I+5x(J+K+L+M+N)		Cost per patient, retreatment (without CT simulation), 5x 4Gy	2.371,08 €
A+B+C+D+E+F+G+H+I+J+K+L+M+N		Cost per patient, 1x 8Gy	1.485,80 €
A+B+C+D+F+G+H+I+J+K+L+M+N		Cost per patient, retreatment (without CT simulation), 1x 8Gy	1.445,92 €

Table S2. Radiotherapy – Inpatient codes and simulation for a 14-day length of stay (DRG 154A)

Code	Description
C79.5 (ICD)	Secondary malignant neoplasm of bone and bone marrow
Z51.0 (ICD)	Radiotherapy session
8-528.6 (OPS)	Irradiation simulation for external beam irradiation and brachytherapy: CT-guided simulation for external beam irradiation
8-529.3 (OPS)	Radiation planning for percutaneous irradiation and brachytherapy: radiation planning for intensity modulated radiotherapy
8-529.4 (OPS)	Radiation planning, fusion with CT and MRI
8-527.2 (OPS)	Aid for fixation, complex
3-990 (OPS)	Computer-aided image data analysis with 3D evaluation
3-995 (OPS)	Dosimetry for therapy planning
5x 8-520.0 (OPS)	Each irradiation, cave: Grouping each on 5 different days
5x 8-522.d1 or 8-522.91 (alternative code)	
Length of stay (14 days)	Total charges: 6409,71€
Length of stay (10 days)	Total charges: 5864,15€ (without 8-528.6 (OPS))

Table S3. Magnetic Resonance Imaging-guided High-Intensity Focused Ultrasound (MR-HIFU) – Inpatient codes and simulation for a 2-day length of stay

Code	Description
C79.5	Secondary malignant neoplasm of bone and bone marrow
5-789.7 (OPS)	Other operations on bone: Destruction, by magnetic resonance guided focused ultrasound [MRgFUS]
3-826 (OPS)	Magnetic resonance imaging of the musculoskeletal system with contrast material
8-900 (OPS)	Intravenous anesthesia
Total charges: 3429.53 €	

MRgFUS synonym for MR-HIFU

SM 2 Assessment of the Validation Status of Health Economic decision models (AdViSHE)

The validation process of the model is reported below according to the questions of the AdViSHE checklist (Vemer, Corro Ramos, van Voorn, Al, & Feenstra, 2016), which is divided in 4 parts:

Part A: Validation of the conceptual model (2 questions)

A1/ Face validity testing (conceptual model): Have experts been asked to judge the appropriateness of the conceptual model?
Experts with different backgrounds and expertise were asked to judge the appropriateness of the conceptual model. SYY, HG, CBos, HMV and GB have extensive expertise in MR-HIFU in Germany. BAB, CB are German radiation oncologists. In this step, one main issue raised was that we had not considered in a first draft the single-fraction EBRT (1x 8Gy). After discussion with experts, we decided to add a proportion of patients being treated with 1x 8Gy in the base case and sensitivity analysis.
A2/ Cross validity testing (conceptual model): Has this model been compared to other conceptual models found in the literature or clinical textbooks?
The concept of the model was developed based in similar models comparing different strategies to the treatment of bone metastases. For instance, the health states considered are similar and the transitions

and equivalent to other Markov models. The assumption regarding opioid intake (oxycodone) in all states except for complete pain relief was also applied in other models.

Part B: Input data validation (2 questions)

B1/ Face validity testing (input data): Have experts been asked to judge the appropriateness of the input data?
All authors were asked to judge the clinical and effectiveness data. In this step, the following issues were raised by experts: 1. Whether the retreatment rate applied to strategy A was appropriate. • Due to lack of better data we kept the initial assumption. We tested a range of retreatment rates in sensitivity analyses. 2. If the data concerning EBRT practices and costs in Germany are possibly outdated, and that single-fraction should be included. • We corrected the base case according to expert opinion (adopting a more conservative approach of the proportion of outpatient EBRT– 70% instead of 60%- and also considering the single-fraction EBRT as treatment alternative).
B2/ Model fit testing: When input parameters are based on regression models, have statistical tests been performed?
We adjusted yearly values to fit the model's monthly cycles and transformed rates into probabilities. These calculations were done by JSCG and reviewed by a second model expert (DM) and a statistician (AS).

Part C: Validation of the computerized model (4 questions)

C1/ External review: Has the computerized model been examined by modelling experts?
Yes. The computerized model was checked by a modelling expert (DM), after data imputation by JSCG.
C2/ Extreme value testing: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors?
To detect coding errors, we tested extreme values for cost data and utility data. Extreme values for proportions of outpatient EBRT and single fration EBRT are reported in the supplementary material
C3/ Testing of traces: Have patients been tracked through the model to determine whether its logic is correct?
Yes, we reviewed individual trials to check for if the events occurring during patients' lifetime were plausible. We used trackers (retreatment and fractures) to identify at cohort level if the model's logic was correct.
C4/ Unit testing: Have individual sub-modules of the computerized model been tested?
Yes. We tested and reported alternative scenarios (e.g., all patients undergoing MR-HIFU as first-line treatment, and all patients undergoing single-fraction EBRT).

Part D: Operational validation (4 questions)

D1/ Face validity testing (model outcomes): Have experts been asked to judge the appropriateness of the model outcomes?
Yes. The appropriateness of model outcomes was judged by all authors.
D2/ Cross validation testing (model outcomes): Have the model outcomes been compared to the outcomes of other models that address similar problems?
Partially done, the model concept and data applied was similar to other models, but there was limited comparability with other models regarding results, since this is the first model to present the comparison MR-HIU vs. EBRT.

D3/ Validation against outcomes using alternative input data: Have the model outcomes been compared to the outcomes obtained when using alternative input data?
Yes. We conducted several structural sensitivity analyses, reported in the main manuscript and in the supplementary material.
D4/ Validation against empirical data: Have the model outcomes been compared to empirical data?
Not applicable.

SM 3 Value of Information (VOI) Analysis

The expected value of perfect information (EVPI) is the difference between the expected value of a decision made with perfect information and the value of the decision made with current evidence (Fenwick et al., 2020). While the EVPI computes all input parameters simultaneously, the expected value of perfect partial information (EVPPI) quantifies how individual parameters or parameters sets contribute to decision uncertainty (Fenwick et al., 2020). A hypothetical willingness-to-pay (WTP) of €20.000 was set to calculate the EVPI and EVPPI in terms of net monetary benefits (NMB). The PSA results were inputted to the Sheffield Accelerated Value of Information (SAVI), which uses regression-based methods to calculate the impact of parameter sets on decision uncertainty. For sets with up to five parameters, the GAM regression method is used. For subsets with five or more parameters the GP regression method is used (Strong, Oakley, & Brennan, 2014).

Because MR-HIFU and radiotherapy are rapidly evolving technologies, the time horizon for the VOI analysis was defined at 5 years (i.e., the time in which the information would have most value). To calculate the populational EVPI, the per person EVPI was multiplied by the potential benefit population in Germany. The potential beneficial population (N) was calculated as:

$$N = P_0 + \sum_{t=0}^{T} \frac{I_t}{(1+r)^t}$$

In that P_0 = prevalent population at time t = 0, I_t = incident population at time t, r = discount rate (defined as 3%) (Fenwick et al., 2020).

The prevalence and incidence of stage IV breast cancer, stage IV prostate cancer, and stage IV lung cancer were taken from the German Centre for Cancer Registry Data (Centre for Cancer Registry Data, 2018), as shown in Table S5.

Table S5. Cancer specific prevalence and incidence rates applied to the calculation of the potential benefit population over 5 years

	5-year prevalence	Incidence 2018	Proportion Stage IV	Benefit Population over 5 years
Breast cancer	304,100	69,900	7%	66,453
Prostate Cancer	260,400	65,200	18%	112,355
Lung cancer	91,600	57,220	52%	232,373
Total				411,181

References

Centre for Cancer Registry Data. (2018). Cancer in Germany Retrieved from https://www.krebsdaten.de/

Fenwick, E., Steuten, L., Knies, S., Ghabri, S., Basu, A., Murray, J. F., . . . Rothery, C. (2020). Value of Information Analysis for Research Decisions-An Introduction: Report 1 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force. *Value Health, 23*(2), 139-150. doi:10.1016/j.jval.2020.01.001

Strong, M., Oakley, J. E., & Brennan, A. (2014). Estimating multiparameter partial expected value of perfect information from a probabilistic sensitivity analysis sample: a nonparametric regression approach. *Med Decis Making, 34*(3), 311-326. doi:10.1177/0272989x13505910

Vemer, P., Corro Ramos, I., van Voorn, G. A., Al, M. J., & Feenstra, T. L. (2016). AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users. *Pharmacoeconomics, 34*(4), 349-361. doi:10.1007/s40273-015-0327-2

SM 4 Deterministic sensitivity analysis (DSA) results

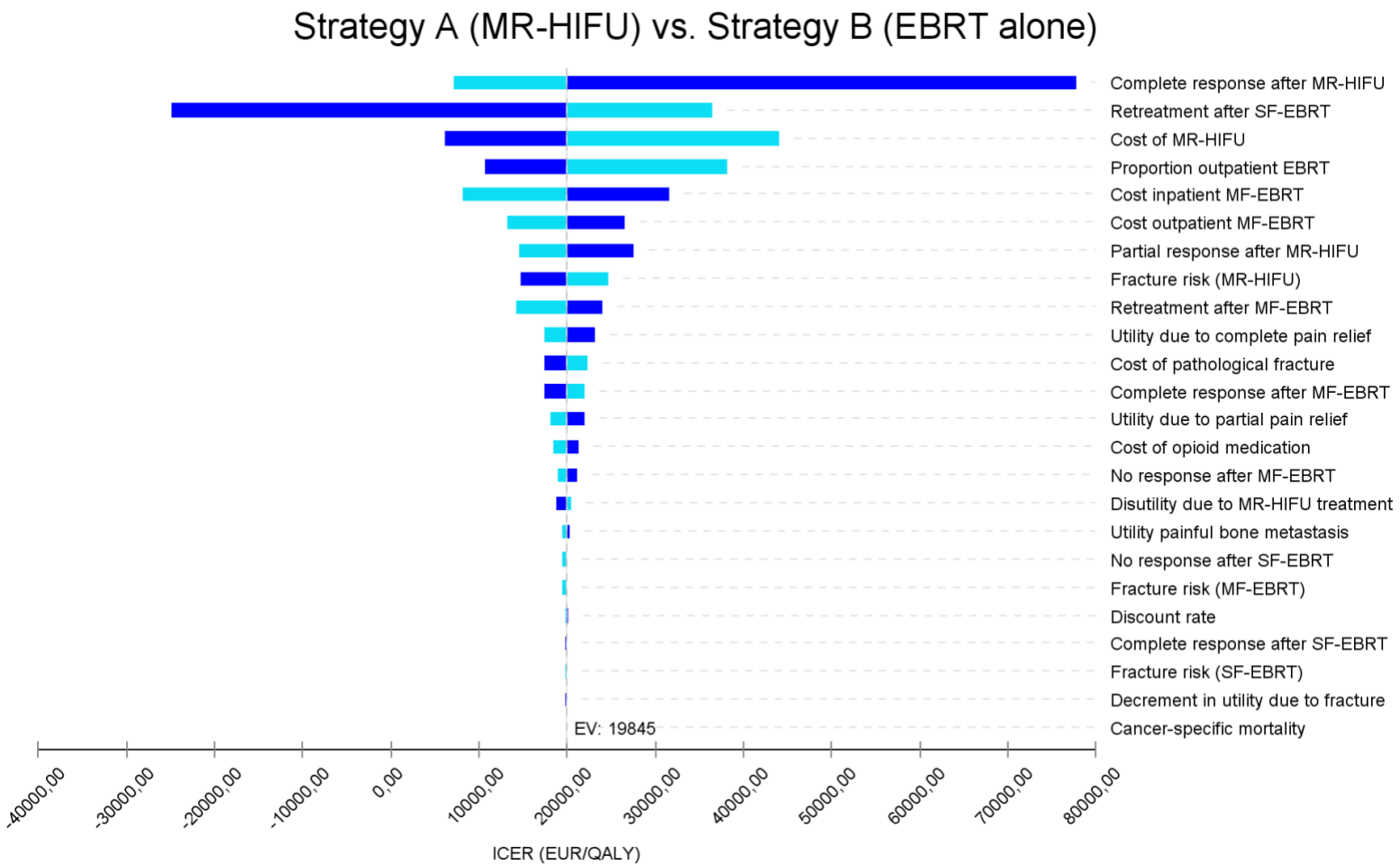

Figure S1. Deterministic sensitivity analyses for patients with bone metastases. The tornado diagrams show the results of deterministic sensitivity analyses (i.e., effect on the ICER by varying one model input parameter at a time, the higher values are represented by light blue bars, lower values by dark blue bars). Abbreviation: ICER: Incremental cost-effectiveness ratio.

Table S6 Results from structural sensitivity analysis

Proportion of 1x8Gy (at both strategies)						
	Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (QALY)	Incr.Effectiveness (QALY)	ICER (€/QALY)
0%	Strategy B	8,318	-	0.939	-	-
	Strategy A	8,631	313	0.961	0.022	14,369
25%	Strategy B	7,783	-	0.944	-	-
	Strategy A	8,323	540	0.961	0.017	31,731
50%	Strategy B	7,275	-	0.950	-	-
	Strategy A	8,010	734	0.961	0.011	68,827
75%	Strategy B	6,720	-	0.950	-	-
	Strategy A	7,676	957	0.960	0.010	98,580
100%	Strategy B	6,214	-	0.954	-	-
	Strategy A	7,388	1174	0.961	0.01	168,392
Proportion of outpatient EBRT (at both strategies)						
	Strategy	Cost (EUR)	Incremental Cost (EUR)	Effectiveness (QALY)	Incr.Effectiveness (QALY)	ICER (EUR/QALY)
0%	Strategy B	9,672	-	0.961	-	-
	Strategy A	10,381	709	0.941	-0.020	dominated
20%	Strategy B	9,190	-	0.961	-	-
	Strategy A	9,437	247	0.941	-0.020	dominated
50%	Strategy A	8,493	-	0.941	-	-
	Strategy B	8,707	215	0.961	0.020	10,664
80%	Strategy A	7,548	-	0.941	-	-
	Strategy B	8,225	676	0.961	0.020	33,615
100%	Strategy A	6,604	-	0.941	-	-
	Strategy B	7,742	1138	0.961	0.020	56,566
Retreatment rate (at strategy A)						
	Strategy	Cost (EUR)	Incremental Cost (EUR)	Effectiveness (QALY)	Incr.Effectiveness (QALY)	ICER (EUR/QALY)
8%	Strategy A	8,115	-	0.941	-	-
	Strategy B	8,500	385	0.961	0.021	18,531
16%	Strategy A	8,115	-	0.941	-	-
	Strategy B	9,181	1066	0.969	0.028	38,252
24%	Strategy A	8,115	-	0.941	-	-
	Strategy B	9,722	1607	0.978	0.037	43,095
32%	Strategy A	8,115	-	0.941	-	-
Cost-covering lump-sums MR-HIFU costs (Simões Corrêa Galendi et al., 2022)						
Mean:5147	Strategy A	8,115		0,937		
	Strategy B	9,663	1,548	0,957	0,020	77,650
Lower:4092	Strategy A	8,115		0,937		
	Strategy B	8,958	843	0,957	0,020	42,253
Upper:5876	Strategy A	8,115		0,937		
	Strategy B	10,151	2,036	0,957	0,020	102,109

SM 5 Expected value of partial perfect information (EVPPI) results

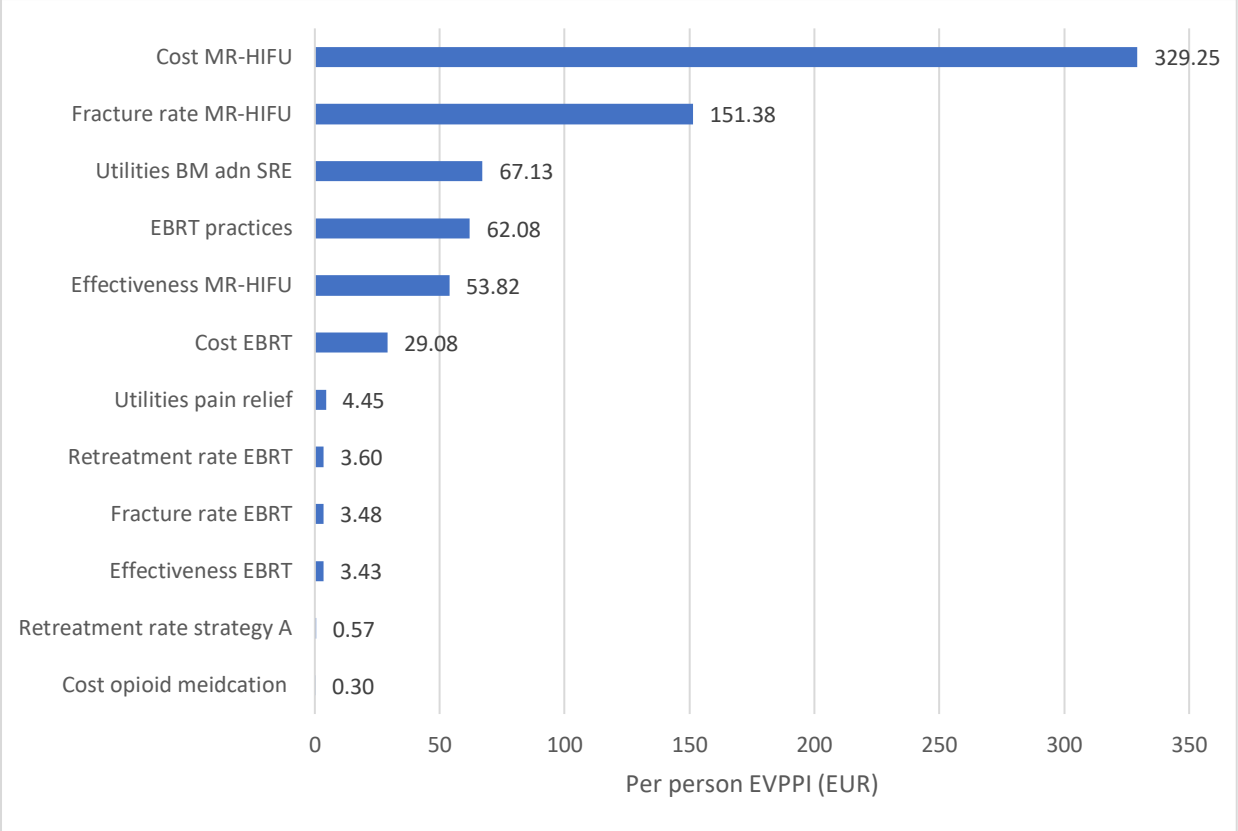

Figure S2. Per person EVPPI for parameter sets. Abbreviations: EVPPI: Expected value of partial perfect information, MR-HIFU: Magnetic resonance-guided High-Intensity Focused Ultrasound, EBRT: External Beam radiotherapy, BM: Bone metastases, SKE: Skeletal-related events.

References

Simões Corrêa Galendi, J., Yeo, S. Y., Simic, D., Grüll, H., Stock, S., & Müller, D. (2022). A time-driven activity-based costing approach of magnetic resonance-guided high-intensity focused ultrasound for cancer-induced bone pain. *Int J Hyperthermia, 39*(1), 173-180. doi:10.1080/02656736.2021.2023768

Appendix

Supplementary material to chapter VI

Contents

SM 1 Informed Consent and participant questions

You have been invited to participate in web-based participatory research, which is part of the FURTHER Project - a Horizon 2020 Project, Grant Number 825859.

By accepting this informed consent, you acknowledge that your participation is voluntary and that the results of this project may be published in an aggregate manner.

For this project, participants will be asked to contribute to the following phases: (i) Brainstorming with the group based on the focus prompt; (ii) Rating and sorting the ideas generated by the group. You will also be asked to provide non-identifying information about yourself. Your participation is confidential, and your input will be made available to other participants anonymously.

You will be reminded to come back to our platform when inputs from other participants are available and when there are new activities open for you. You may participate in the entire project or in one of the two phases.

☐ ACCEPT
☐ DECLINE

Table 1A. Demographic questions

	Description	Question	Closed Answers
1	FURTHER Consortium	Are you already a member of the FURTHER Consortium?	• Yes • No
2	Country	In which country are you based?	• The Netherlands • Germany • Italy • Finland • Other
3	Expertise	How would you describe your expertise in relation to MR-HIFU provision?	• **Patient**, caretaker or patient representative • **Expertise on performing HIFU treatment** (e.g. radiologist, interventional radiologist) • **Expertise on other medical specialties** (e.g. radiation oncologist, radiotherapist, oncologist, gynecologist, orthopedic surgeon, anesthesiologist) • **Expertise on the HIFU technology** (e.g. research scientist on experimental imaging, clinical researcher, physicist) • **Expertise on the Value Proposition/ Financial aspects** (e.g. representative for a regulatory agency, or Health Technology Assessment agency, hospital manager, technology provider or developer, market access, entrepreneurial service organization)
4	Educational background	What is your educational/academic background?	• Radiology • Radiation Oncology or Radiotherapy • Oncology • Orthopedic Surgery • Anesthesiology • Biological Engineering • Physics • Health Economics • Business / Public administration • Epidemiology • Other
5	Prior Knowledge	How would you rate your knowledge on the latest evidence on MR-HIFU for cancer induced bone pain?	• Excellent • Good • Regular • Low • None

SM 2 Editing statements

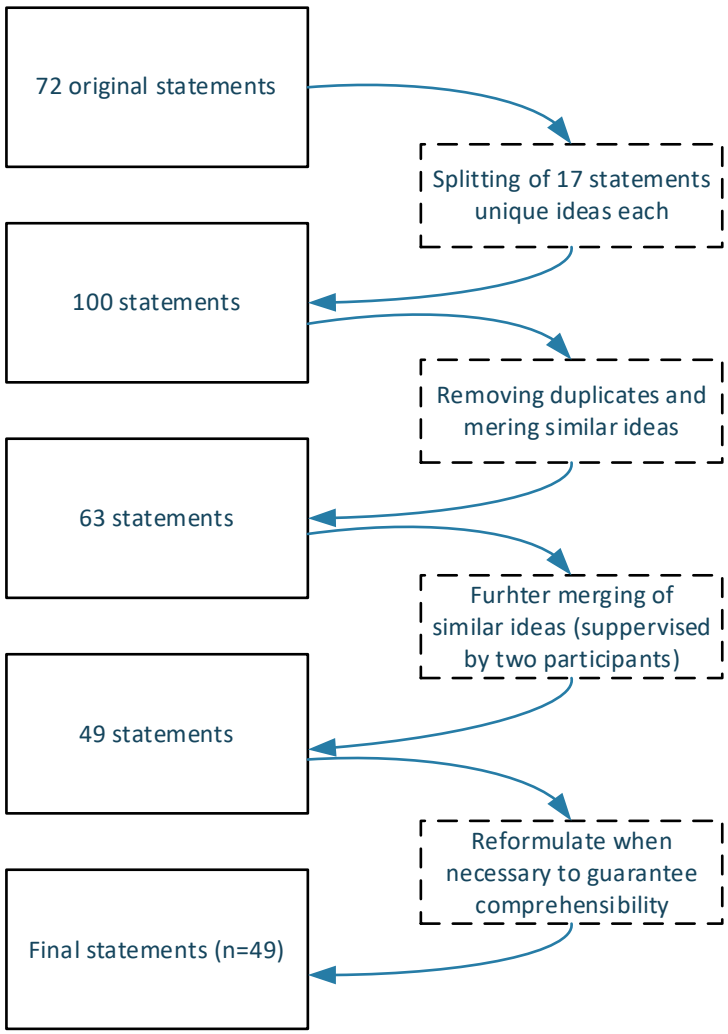

Figure 1A Flowchart the process of splitting and merging statements

Table 2A. Examples of splitting and merging of statements

Original statement(s)	**Adjusted statement(s)**
Splitting	
• Difficult patient recruitment, due to the large range in referring medical specialists and their unfamiliarity with HIFU	• Difficult patient recruitment, due to the large range in referring medical specialists • Unfamiliarity of referring physicians with HIFU
Removing duplicates	
• Lack of reimbursement • Missing reimbursement is an issue in many countries making the adoption of MR-HIFU difficult or impossible • Reimbursement inside the hospital is essential	• Reimbursement of MR-HIFU as inpatient procedure • Reimbursement of MR-HIFU as outpatient procedure

• Reimbursement in ambulatory care is essential	
Comprehensibility	
• organizing GA in a radiology suite (where the MRI is) is an extra cost for the equipment (can be solved once and for all)	• High additional costs related to general anesthesia [removed abbreviation, shortened the statement]

SM 3 Point Map

Figure 2A. Point Map: statements (and respective identification numbers) plotted on an x–y chart.

SM 4 Statements per Cluster

Table 3A. Statements per cluster and average perceived importance.

Cluster		**Average of perceived importance of each statement**					**Coherence of perception among countries**
ID	Statement	IT	NL	DE	FI	All participants	
(1)	**Competitive treatments**	**1,29**	**1,36**	**1,71**	**1,07**	**1,36**	**0,07**
1	Conflict of interest from referring physicians favoring other treatment alternatives	2,00	2,50	3,00	1,67	2,29	0,34
6	Availability of ultrasound-guided HIFU as a competitive treatment alternative	1,18	2,00	2,00	2,00	1,72	0,17
16	Availability of cryotherapy as a competitive treatment alternative	0,73	0,86	1,29	0,50	0,84	0,11
17	Availability of electro chemotherapy as a competitive treatment alternative	1,18	0,71	1,14	0,50	0,94	0,11
18	Availability of embolization as a competitive treatment alternative	1,36	0,71	1,14	0,67	1,03	0,11
(2)	**Physicians' attitude**	**2,44**	**2,58**	**2,50**	**2,25**	**2,45**	**0,02**
13	Unfamiliarity/ lack of knowledge among referring physicians with MR-HIFU as a treatment option	2,55	3,11	3,29	3,17	2,97	0,11
20	Risk avoidance of the medical profession (preference for staying with established treatment methods)	2,18	2,63	2,57	2,00	2,34	0,09
21	Intrinsic inertia to new treatments (due to overload of the medical profession)	2,18	2,00	2,14	1,67	2,03	0,05
24	Limited indication for only a small subgroup of bone metastasis patients	2,82	2,89	2,43	2,50	2,70	0,05
45	Bone metastases patients are often unfit for general anesthesia	2,45	1,88	2,00	2,33	2,19	0,07
14	Difficult patient recruitment, due to large range in referring medical specialists	2,45	3,00	2,57	1,83	2,50	0,23
(3)	**Alignment of resources**	**3,00**	**2,32**	**2,50**	**2,64**	**2,65**	**0,08**
2	Organizational and logistical routine for MR-HIFU within center	2,73	2,78	2,71	2,83	2,76	0,00
28	Availability of centers with HIFU treatment facilities	2,91	2,00	3,14	2,83	2,72	0,25
29	Availability of a hospital bed for overnight stay	2,64	1,78	1,17	1,83	2,06	0,36
31	Frequency of time slots at the MRI dedicated for HIFU	3,36	2,38	2,71	3,00	2,91	0,17
32	Scarcity of MRI resources	2,91	2,00	2,29	1,83	2,34	0,23
43	Availability of anesthesiologist for MR-HIFU procedures	3,45	3,00	2,43	3,50	3,13	0,25
(4)	**Logistics and workflow**	**2,56**	**2,33**	**2,66**	**2,61**	**2,53**	**0,02**
4	Referral routine within center	2,36	2,11	3,14	2,83	2,55	0,21
5	Referral routine to external centers offering MR-HIFU	2,55	2,25	2,57	2,40	2,45	0,02
30	Collaboration between different healthcare professionals	3,00	2,89	2,86	3,17	2,97	0,02

	44	Anesthesiological approaches tailored for MR-HIFU	2,27	2,13	2,14	1,83	2,13	0,03
	46	Lack of an established patient workflow (from HIFU-indication to release of the patient)	2,64	2,25	2,57	2,83	2,56	0,06
(5)	**Technical disadvantages**		**2,27**	**2,04**	**2,46**	**2,17**	**2,24**	0,03
	7	MR-HIFU is a lengthy procedure	2,55	2,67	2,71	2,67	2,64	0,00
	8	Instability of interface of MR scanner with HIFU system	1,73	1,86	2,29	1,67	1,87	0,08
	27	Compatibility of HIFU equipment with the MR scanner delay the setup of treatment facilities	1,82	1,63	2,14	1,83	1,84	0,04
	33	Scarcity of HIFU equipment	3,00	2,00	2,71	2,50	2,59	0,18
(6)	**Radiotherapy as first-line therapy**		**2,85**	**2,95**	**3,05**	**2,67**	**2,89**	**0,03**
	7	HIFU is less flexible with respect to different anatomical regions compared to radiotherapy	2,64	2,63	2,86	2,67	2,69	0,01
	26	Competitive logistical advantage of radiotherapy	2,82	3,11	3,00	2,67	2,91	0,04
	47	HIFU treatment procedure complexity compared to radiotherapy	3,09	3,11	3,29	2,67	3,06	0,07
(7)	**Aggregating knowledge & Improving awareness**		**2,65**	**2,61**	**2,61**	**2,58**	**2,62**	**0,00**
	3	Inter-center knowledge exchange	2,27	2,25	2,00	3,00	2,34	0,19
	12	Clear position of MR-HIFU in clinical guidelines	3,09	3,11	3,29	3,33	3,18	0,02
	15	Synergy of incorporating MR-HIFU for other clinical indications and treatment regimes	2,64	2,63	3,00	2,50	2,69	0,05
	39	Users' perception of lack of cost-effectiveness for pain palliation "only"	2,60	2,44	2,14	1,50	2,25	0,24
(8)	**Clinical effectiveness**		**2,50**	**3,19**	**3,19**	**3,33**	**2,99**	**0,14**
	9	Safety profile of MR-HIFU (few or no side effects)	2,36	2,67	3,14	3,17	2,76	0,15
	34	Clinical evidence from randomized clinical trials on the effectiveness of MR-HIFU	2,50	3,56	3,57	3,50	3,22	0,27
	35	Experience/ Observation of positive outcomes after treatment with MR-HIFU	2,64	3,33	2,86	3,33	3,00	0,12
(9)	**Patients' preferences**		**2,55**	**2,94**	**2,79**	**2,67**	**2,73**	**0,03**
	19	Enthusiasm for the non-invasive treatment	2,45	3,00	2,43	2,33	2,58	0,09
	22	Patient preference for an outpatient procedure	2,82	2,33	3,14	2,17	2,64	0,20
	23	Fast recovery after treatment	2,45	2,75	2,86	3,17	2,75	0,09
	36	Superior pain relief compared to radiotherapy	2,45	3,67	2,71	3,00	2,94	0,28
(10)	**Reimbursement**		**2,33**	**3,00**	**3,05**	**1,83**	**2,56**	**0,34**
	10	Reimbursement of MR-HIFU as inpatient procedure	2,73	3,13	2,86	1,67	2,66	0,41
	11	Reimbursement of MR-HIFU as outpatient procedure	1,82	3,00	3,43	2,00	2,50	0,60
	41	Reimbursement to offset the costs of supporting personnel (anesthesia)	2,45	2,88	2,86	1,83	2,53	0,24
(11)	**Cost-effectiveness**		**2,36**	**2,56**	**2,64**	**2,73**	**2,55**	**0,02**
	40	Evidence on cost-effectiveness in relation to standard of care	2,55	3,25	3,00	3,00	2,91	0,09

	49	Reduced costs compared to surgery	2,18	1,88	2,29	2,50	2,19	0,07
(12)	**Hospital costs**		**2,44**	**2,33**	**2,75**	**2,25**	**2,45**	**0,05**
	37	Costs of equipment maintenance	2,45	2,25	2,86	2,00	2,41	0,13
	38	Running costs	2,50	2,75	3,14	2,50	2,71	0,09
	42	High additional costs related to general anesthesia	2,18	2,44	2,00	2,33	2,24	0,04
	48	Costs of initial setup (purchase of equipment, installation, etc.)	2,64	1,88	3,00	2,17	2,44	0,25

Abbreviations: IT: Italy, NL: the Netherlands, DE: Germany, FI: Finland

SM5 Statements located in the northeast quadrant of the Go-Zone

Table 4A. Statements located in the northeast quadrant of the Go-Zone (sorted by cluster)

Cluster	**Number (%) of statements in the Go-zone**	**ID**	**Statement**
(2) Physicians' attitude	2(33%)	13	Unfamiliarity/ lack of knowledge among referring physicians with MR-HIFU as a treatment option
		14	Difficult patient recruitment, due to large range in referring medical specialists
(3) Alignment of resources	3(50%)	2	Organizational and logistical routine for MR-HIFU within center
		28	Availability of centers with HIFU treatment facilities
		31	Frequency of time slots at the MRI dedicated for HIFU
(4) Logistics and workflow	3 (60%)	4	Referral routine within center
		30	Collaboration between different healthcare professionals
		46	Lack of an established patient workflow (from HIFU-indication to release of the patient)
(5) technical disadvantages	1(25%)	33	Scarcity of HIFU equipment
(6) Radiotherapy as first-line therapy	2(67%)	25	HIFU is less flexible with respect to different anatomical regions compared to radiotherapy
		47	HIFU treatment procedure complexity compared to radiotherapy
(7) Aggregating knowledge & Improving Awareness	2 (50%)	12	Clear position of MR-HIFU in clinical guidelines
		15	Synergy of incorporating MR-HIFU for other clinical indications and treatment regimes
(8) clinical effectiveness	3 (100%)	9	Safety profile of MR-HIFU (few or no side effects)
		34	Clinical evidence from randomized clinical trials on the effectiveness of effectiveness MR-HIFU
		35	Experience/ Observation of positive outcomes after treatment with MR-HIFU
(9) Patients' preferences	4 (100%)	19	19 Enthusiasm for the non-invasive treatment
		22	Patient preference for an outpatient procedure preferences
		23	Fast recovery after treatment
		36	Superior pain relief compared to radiotherapy
(10) Reimbursement	1 (33%)	11	Reimbursement of MR-HIFU as outpatient procedure
(11) Cost-effectiveness	1 (50%)	40	Evidence on cost-effectiveness in relation to standard of care

Doctoral student's declaration of contribution

Hiermit versichere ich, dass ich den wesentlichen Beitrag der Publikationen geleistet habe. Übersicht der Publikationen und den von der Doktorandin geleisteten Beitrag zu den Publikationen:

Publikation 1

A time-driven activity-based costing approach of magnetic resonance-guided high-intensity focused ultrasound for cancer-induced bone pain

Julia Simões Corrêa Galendi, Sin Yuin Yeo, Dusan Simic, Holger Grüll, Stephanie Stock, Dirk Müller

International Journal of Hyperthermia [Impact Factor: 3.753]

Beitrag der Doktoradin: JSCG, DS und SS haben das Konzept entwickelt. DM hat zum Studiendesign beigetragen und kontinuierlich Feedback gegeben. JSCG und SY haben Daten erhoben. JSCG hat die Datenanalyse durchgeführt, und DM hat dabei unterstützt. HG und DM haben die Plausibilität der Ergebnisse geprüft. JSCG hat das Manuskript geschrieben. SY, HG, DS, SS und DM haben das Manuskript kritisch gelesen, revidiert und der finalen Version des Manuskripts zur Publikation zugestimmt.

Publikation 2

Early economic modeling of magnetic resonance image-guided High-Intensity focused ultrasound compared to radiotherapy for pain palliation of bone metastases

Julia Simões Corrêa Galendi, Sin Yuin Yeo, Holger Grüll, Grischa Bratke, Dennis Akuamoa-Boateng, Christian Baues, Clemens Bos, Helena M Verkooijen, Arim Shukri, Stephanie Stock, Dirk Müller

Frontiers in Oncology [Impact Factor: 5.738]

Beitrag der Doktoradin: JSCG hat das Konzept entwickelt, SS und DM haben dabei unterstützt. JSCG, SY, DA-B haben die Eignung der Literatur geprüft. JSCG hat das Model entwickelt und die Input Parameter eingepflegt. DM und AS haben die technische Validierung durchgeführt. DA-B, CB, HG, SY, CBo und HV haben die Plausibilität des Models geprüft. JSG hat die Datenanalyse durchgeführt, und DM hat dabei unterstützt.

JSCG hat das Manuskript geschrieben. SY, HG, GB, DA-B, CBa, CBo, HV, AS, SS und DM haben das Manuskript kritisch gelesen, revidiert und der finalen Version des Manuskripts zur Publikation zugestimmt.

Publikation 3

Factors influencing the uptake of magnetic resonance imaging-guided High-Intensity focused ultrasound for painful bone metastases in Europe, a group concept mapping study

Julia Simões Corrêa Galendi, Ann-Cathrine Siefen, Debora Moretti, Sin Yuin Yeo, Holger Grüll, Grischa Bratke, Alessio Giuseppe Morganti, Alberto Bazzocchi, Chiara Gasperini, Roberto Blanco, Mira Huhtala, Ingrid M. Nijholt, Martijn F. Boomsma, Clemens Bos, Helena M. Verkooijen, Francesca de Felice, Dirk Müller, Stephanie Stock
International Journal of Environmental Research and Public Health [Impact Factor 4.614]

Beitrag der Doktoradin: JSCG hat das Konzept entwickelt. DMo hat zum Studiendesign beigetragen und kontinuierlich Feedback gegeben. SYY, HG, GB, AGM, AB, CG, FF, RB, MH, IMN, MFB, CB, HMV and DM haben die Teilnehmer ausgesucht und die Plausibilität der Ergebnisse geprüft. JSCG and ACS haben die Analyse durchgeführt. JSCG hat das Manuskript geschrieben. ACS, DMo, SYY, HG, GB, AGM, AB, CG, FF, RB, MH, IMN, MFB, CB, HMV, DM and SS haben das Manuskript kritisch gelesen, revidiert und der finalen Version des Manuskripts zur Publikation zugestimmt.

Eidesstattliche Erklärung

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertationsschrift selbstständig und ohne die Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Stellen - einschließlich Tabellen, Karten und Abbildungen -, die wörtlich oder sinngemäß aus veröffentlichten und nicht veröffentlichten anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, sind in jedem Einzelfall als Entlehnung kenntlich gemacht. Ich versichere an Eides statt, dass diese Dissertationsschrift noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen - noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss der Promotion nicht ohne Genehmigung der / des Vorsitzenden des IPHS-Promotionsausschusses vornehmen werde. Die Bestimmungen dieser Ordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Prof. Dr. med. Stephanie Stock betreut worden.

Darüber hinaus erkläre ich hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten der Universität zu Köln gelesen und sie bei der Durchführung der Dissertation beachtet habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen.

Übersicht der Publikationen:

[1] Simões Corrêa Galendi J, Yeo SY, Simic D, Grüll H, Stock S, Müller D. A time-driven activity-based costing approach of magnetic resonance-guided high-intensity focused ultrasound for cancer-induced bone pain. *Int J Hyperthermia.* 2022; 39(1):173-180. doi:10.1080/02656736.2021.2023768. PMID: 35021942.

[2] Simões Corrêa Galendi J, Yeo SY, Grüll H, Bratke G, Akuamoa-Boateng D, Baues C, Bos C, Verkooijen HM, Shukri A, Stock S, Müller D. Early economic modeling of magnetic resonance image-guided High-Intensity focused ultrasound compared to radiotherapy for pain palliation of bone metastases. *Front Oncol*. 2022; 12:987546. doi: 10.3389/fonc.2022.987546.

[3] Simões Corrêa Galendi J, Siefen A-C, Moretti DM, Yeo SY, Grüll H, Bratke G, Morganti AG, Bazzocchi A, Gasperini C, De Felice F, Blanco Sequeiros R, Huhtala M, Nijholt IM, Boomsma MF, Bos C, Verkooijen HM, Müller D, Stock S. Factors Influencing the Adoption of Magnetic Resonance-Guided High-Intensity Focused Ultrasound for Painful Bone Metastases in Europe, A Group Concept Mapping Study. International Journal of Environmental Research and Public Health. 2023; 20(2):1084. https://doi.org/10.3390/ijerph20021084

Ich versichere, dass ich alle Angaben wahrheitsgemäß nach bestem Wissen und Gewissen gemacht habe und verpflichte mich, jedmögliche, die obigen Angaben betreffenden Veränderungen, dem IPHS-Promotionsausschuss unverzüglich mitzuteilen.

Köln 29.03.2023 Julia Simões Corrêa Galendi