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Original Research Article

Combining radiotherapy and focused ultrasound for pain palliation of cancer induced bone pain; a stage I/IIa study according to the IDEAL framework

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ABSTRACT

Background: Cancer induced bone pain (CIBP) strongly interferes with patient's quality of life. Currently, the standard of care includes external beam radiotherapy (EBRT), resulting in pain relief in approximately 60% of patients. Magnetic Resonance guided High Intensity Focused Ultrasound (MR-HIFU) is a promising treatment modality for CIBP.

Methods: A single arm, R-IDEAL stage I/IIa study was conducted. Patients presenting at the department of radiation oncology with symptomatic bone metastases in the appendicular skeleton, as well as in the sacrum and sternum were eligible for inclusion. All participants underwent EBRT, followed by MR-HIFU within 4 days. Safety and feasibility were assessed, and pain scores were monitored for 4 weeks after completing the combined treatment.

Results: Six patients were enrolled. Median age was 67 years, median lesion diameter was 56,5 mm. In all patients it was logistically possible to plan and perform the MR-HIFU treatment within 4 days after EBRT. All patients tolerated the combined procedure well. Pain response was reported by 5 out of 6 patients at 7 days after completion of the combined treatment, and stabilized on 60% at 4 weeks follow up. No treatment related serious adverse events occurred.

Conclusion: This is the first study to combine EBRT with MR-HIFU. Our results show that combined EBRT and MR-HIFU in first-line treatment of CIBP is safe and feasible, and is well tolerated by patients. Superiority over standard EBRT, in terms of (time to) pain relief and quality of life need to be evaluated in comparative (randomized) study.

1. Introduction

Cancer induced bone pain (CIBP) strongly interferes with quality of life and daily functioning of cancer patients [1,2]. For patients suffering from bone metastases, it is crucial to provide fast and sufficient pain relief to optimize quality of life. The current standard of care for pain palliation in patients with uncomplicated painful bone metastases includes external beam radiotherapy (EBRT) [3–7]. EBRT is a well-established treatment option, but usually takes about four weeks to induce adequate pain relief, and 30–40% of patients show no response at all [8–11]. Moreover, approximately 50% of the responders experience recurrent pain and re-irradiation is only effective in 58% of patients [8,11]. As such, there is ample room for improvement of local management of CIBP.

Magnetic Resonance guided High Intensity Focused Ultrasound (MR-HIFU) is a noninvasive image-guided treatment modality with

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many potential applications in oncology [12]. MR-HIFU delivers acoustic energy to heat tissue in a target area to ablative temperatures. The hypothetical mode of action of MR-HIFU for CIBP is ablation of periosteal nerves and tumor debulking [21]. MR-HIFU aims at palliative pain treatment and has been shown to be effective in inducing rapid and long-lasting pain relief with response rates ranging from 67% to 88% [13–20].

The role of MR-HIFU in the first-line management of CIBP has not yet been determined. In a white paper on focused ultrasound, the need to explore the value of MR-HIFU as a primary therapeutic option for CIBP was stated [22]. Moreover, combining MR-HIFU with EBRT may result in an improved pain response as compared to what each treatment individually may achieve, therefore the exploration of a combined approach was advocated. The rationale behind combining EBRT with MR-HIFU is twofold. Firstly, MR-HIFU may induce a faster pain response, as shown by a phase III sham-trial comparing MR-HIFU treatment to a placebo treatment in patients who had not responded to radiotherapy. In this study response occurred within three days after MR-HIFU treatment [13]. Secondly, there may be a complimentary effect of MR-HIFU and EBRT, as both treatments have a slightly different mechanism of action [21]. Until now, there is no evidence available on the feasibility or safety of combined EBRT and MR-HIFU treatment.

The main objective of the current study was to evaluate the feasibility of combined EBRT and MR-HIFU treatment within a narrow time window in terms of patient tolerance and hospital logistics. Safety and pain response were assessed as well.

2. Methods

2.1. Study design and patient selection

This single arm intervention study for the combination of EBRT and MR-HIFU was conducted in the University Medical Center Utrecht (UMCU) and Isala Hospital Zwolle, the Netherlands. The study was approved by the ethical board of the UMCU and was registered in the ClinicalTrials.gov database under trial number NCT04310410.

The study was conducted following the R-IDEAL recommendations for systematic clinical evaluation of technical innovations in radiation oncology [27]. R-IDEAL identifies has five stages and is applicable to innovations in the radiation oncology setting. The current study entails stages I and IIa. The aim of stage I was to demonstrate proof of concept of the combination treatment. After assessment of feasibility and safety by an independent safety committee board consisting of three experts in the field of pain palliation for bone metastases, the study continued to stage IIa. In stage IIa, safety and feasibility were further evaluated, and the workflow of the new treatment strategy was optimized.

Patients referred to the radiation oncology departments of both centres were eligible for inclusion when they were aged 18 years or older, had symptomatic uncomplicated bone metastases with a pain score of $\geq$4 on a 11-point numeric rating scale (NRS, 0–10) with one predominantly painful lesion. This lesion had to be located in the appendicular skeleton, sacrum or sternum, with a maximum dimension of 8 cm and an unobstructed acoustic window on the target lesion had to be achieved. Patients referred for primary course radiotherapy as well as re-irradiation were eligible. Patients were excluded in case of primary bone tumor, poor Karnofsky performance score (<60%), need for surgery in the target area due to instability of the bone metastasis, a curative intent primary oncologic treatment plan, or if contraindications to MR imaging or procedural sedation and analgesia (PSA) were present. Eligibility was assessed in a multidisciplinary setting by a radiation oncologist and interventional radiologist.

2.2. Study procedures

After signed informed consent, patients received single or multiple fraction EBRT followed by MR-HIFU within 4-days after the last EBRT fraction. In Fig. 1 the treatment regimen timeline is depicted visually.

2.2.1. Radiotherapy treatment

All patients underwent EBRT according to the standard of care on a priority base within a maximal period of 7 days after they were referred to the outpatient clinic of the radiation oncology department. The radiation schedule was at the discretion of the treating radiation oncologist. As part of standard treatment preparation, patients underwent a planning CT scan in treatment position. A single dose of 8 Gray (Gy), or a multi-fraction regimen of 20 Gy dispersed over 5 fractions was prescribed to the painful bone metastasis. In case of virtual simulation, the visible lesion received at least 80% of the prescribed dose using single or multiple treatment fields with a dose maximum of 115%. In case of Intensity modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT), plans were accepted if at least 90% of the PTV received 95% of the prescribed dose (V90 > 95%). Typically, a 10-mm isotropic planning target volume (PTV) margin was used. A maximal 3D dose of 110% was allowed. The maximum allowed dose in organs at risk was determined according to local institution's protocol. Position verification was done using cone beam CT at every fraction.

2.2.2. MR-HIFU treatment

MR-HIFU treatment was delivered on a clinical MR-HIFU system (Sonalleve System, V2, Profound Medical Corp, Mississauga, Canada), integrated into a 1.5-T MR scanner (Achieva, Philips Healthcare, Best, The Netherlands). The procedure was performed by interventional radiologists. During treatment preparation, the skin overlying the site of interest was shaved. Premedication consisted of paracetamol (1000 mg), diclofenac (75 mg) and oxycodone (10 mg). During the procedure patients received deep procedural sedation and analgesia (PSA), using propofol, esketamine and/or remifentanyl at the discretion of the PSA specialist. Treatment planning and patient positioning was done on the basis of multi-planar reconstructions of three-dimensional T1 and T2w-spoiled-gradient echo scans. While avoiding critical structures, the HIFU beam path was placed as perpendicular to the cortical bone surface as possible, by rotating the patient and tilting the HIFU transducer. One or more test sonications (0.3–0.6 kJ) were performed after which the treating physician determined the therapeutic acoustic power level for the therapeutic sonications. Maintaining a temperature of at least 55 °C for 1 s as measured by MR-thermometry is considered to deliver a thermal dose high enough to achieve adequate ablation of the periosteum [28,29]. During treatment, real time temperature mapping was used to monitor whether this goal was achieved and to determine completion of treatment. Preferably full lesion surface coverage was achieved by systematically sonicating treatment cells in a contiguous way, respecting cooling times between sonications. After the procedure, a gadolinium-enhanced T1w-scan was acquired. Post-procedural pain was managed with dexamethasone (4 mg) and fentanyl (50–200 μg) and patients were temporarily observed in a recovery room until any and all effects of the sedation wore off. Subsequently, they were transferred to the nursing department and discharged with follow-up in an outpatient setting. Discharge medication consisted of a personalized 3-day regimen with dexamethasone (maximum of 8 mg), oxycodone (maximum of 30 mg) and paracetamol (maximum of 4 g).

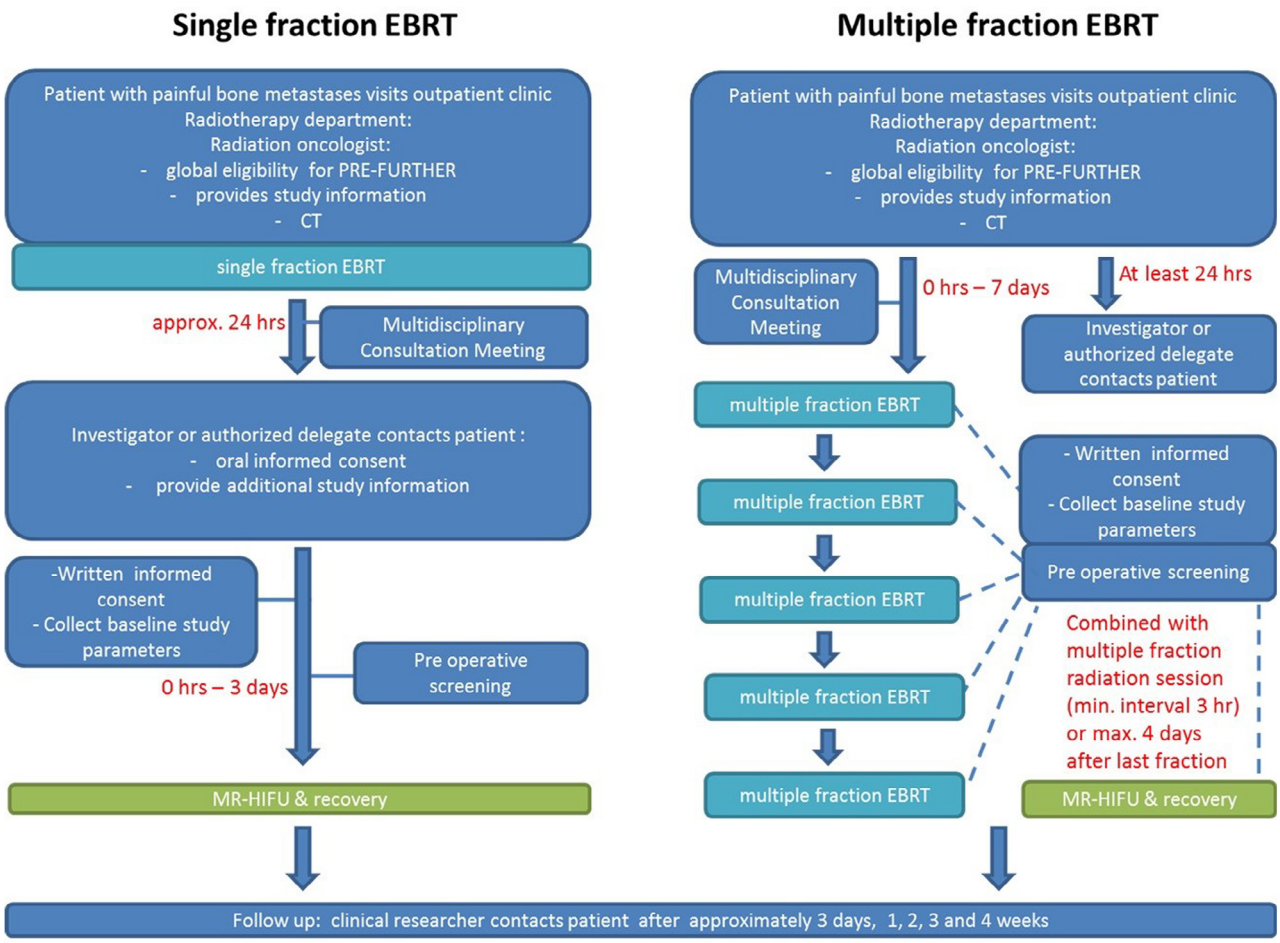

Fig. 1. Schematic flowchart of treatment planning. Participants first received the standard of care, either single- or multiple fraction radiotherapy, followed by MR-HIFU. The MR-HIFU treatment started at least 3 hours after a radiotherapy fraction, and no later than four days after the last fraction.

2.3. Outcomes

The main objective of this study was to evaluate the feasibility of the combined EBRT/MR-HIFU treatment in terms of patient tolerance and hospital logistics. Patient tolerance was assessed 3 days after completion of the combined treatment using a short patient reported experience measure (PREM) questionnaire. Including a scale of 0–10 to rate the MR-HIFU treatment in general and questions about whether or not they experienced waiting times and extra hospital visits as a burden.

In addition, safety and pain response after combined EBRT/MR-HIFU treatment were assessed. For this purpose, patients were contacted by phone to retrieve information about their level of pain and pain medication, 3 days and 1, 2, 3 and 4 weeks after completion of the combined treatment. Toxicity was evaluated and classified according to the Common Toxicity Criteria Adverse Events 5.0 (CTCAE 5.0). Pain scores related to the target lesion treated were measured by patient's self-assessment on an 11-point NRS in the Brief Pain Inventory (BPI) questionnaire [30].

Pain response was defined in concurrence with the international consensus [31] for clinical trial endpoints on bone pain palliation with radiotherapy. Pain responders were defined as patients with a reduction of pain score of at least 2 points at the treated site without increase of analgesic intake, or analgesic intake reduction of at least 25% without increase of pain at the treated site. All other patients were categorized as non-responders.

2.4. Statistical analysis

Descriptive statistical analyses were performed using IBM SPSS statistics, version 24 (IBM Corp. Armonk, N.Y., USA) and R version 3.6.3 (R foundation for statistical computing; https://R-project.org/). Overall response rate was calculated as the proportion of responders of evaluable patients.

3. Results

3.1. Patient characteristics

In stage I of the study, two patients were included. After initial assessment of feasibility and safety by the expert panel safety committee board, four more patients were included in stage IIa. Median age was 67 years (range 53–81 years), 5 patients were male and median Karnofsky performance score ranged between 80 and 90% (Table 1). Primary tumor included prostate carcinoma (N = 3), renal cell carcinoma (N = 1), cholangiocarcinoma (N = 1) and bladder cancer (N = 1). Target lesions were located in the pelvis (N = 4) or extremities (N = 2), and lesion type was lytic (N = 3), blastic (N = 2) or mixed (N = 1). Median lesion maximum diameter was 56.5 mm (range 39–78 mm). Four patients received single fraction radiotherapy (of which one was a re-irradiation) and two received multi-fraction radiotherapy (Table 2).

Table 1
Patient and lesion characteristics on baseline.

Patient	Sex	Age (years)	KPS	Primary tumor	Location	Lesion type	Maximum diameter (mm)*
1	M	62	80	Renal cell	Os ilium	Lytic	48
2	F	53	80	Cholangio	Trochanter minor	Lytic	39
3	M	81	80	Prostate	Os pubis	Mixed	76
4	M	72	80	Bladder	Os pubis	Lytic	65
5	M	76	90	Prostate	Femur	Blastic	40
6	M	59	90	Prostate	SI-joint	Blastic	78

Abbreviations: *KPS* Karnofsky Performance Score, *mm* millimeter, *M* Male, *F* Female, *SI* Sacroiliac.
* As seen on pre-treatment CT imaging.

Table 2
Treatment parameters of received EBRT and MR-HIFU treatments.

Patient	EBRT			Time between treatments* (days)	MR-HIFU			
	Fractionation	Previous radiotherapy	EBRT technique		Duration (min)	Number of sonications	Treated volume (cc)	>50% of target periost ablated□
1	5 × 4 Gy	No	VMAT	0	115	47	8,75	No
2	5 × 4 Gy	No	VSIM	3	88	23	8,38	No
3	1 × 8 Gy	No	VSIM	3	99	30	11,4	Yes
4	1 × 8 Gy	No	VSIM	1	111	31	5,53	Yes
5	1 × 8 Gy	Yes	VMAT	1	88	21	8,38	No
6	1 × 8 Gy	No	VSIM	1	88	32	2,26	Yes

Abbreviations: *EBRT* External Beam Radiotherapy, *MR-HIFU* Magnetic Resonance-High Intensity Focused Ultrasound, *VMAT* Volumetric-Modulated Arc Therapy, *VSIM* Virtual Simulation.
* Time between last received EBRT fraction and MR-HIFU treatment.
□ As visually assessed by the treating interventional radiologist at the end of the treatment.

3.2. Feasibility

In all patients it was logistically possible to perform combined EBRT/MR-HIFU treatment within 4 days. The interval between the last EBRT fraction and MR-HIFU treatment ranged from 4 h to 3 days. In 3 patients it was possible to effectively ablate more than half of the target bone surface as visually assessed by the physician. The extent to which the target bone surface could be ablated depended on visibility, extension, accessibility, and heating specifications of the target lesion, in relation to procedure time restraints such as constraints of the sedation time and MR availability. In Fig. 2 an example of treatment imaging is depicted. Challenges for feasibility were mostly linked to the well-established workflow and one-stop-palliation planning of standard radiotherapy. It was especially challenging to plan the rather complex MR-HIFU procedure within 4 days after the last radiotherapy fraction, due to the limited availability of the MR-scanner and specialized personnel. One or two regular weekly MR-HIFU slots ensured rapid planning and made the combination treatment compatible with the daily practice of the radiation oncology department.

Patient tolerated the combined EBRT/MR-HIFU treatment well. All patients indicated to be satisfied and rated the combination treatment with an average of 8.4 on a scale from 0 to 10 (range 7–10). Four patients paid extra visits to the hospital to be able to undergo the combination treatment. One of these 4 patients experienced this as a minor inconvenience.

3.3. Safety

The combination treatment was safely completed in all patients. The median total sonication time (including cooling times) was 94 min (range 88–115 min). Minor adverse events included a skin abrasion due to positioning (N = 1), and temporary post-procedural pain increase (N = 4), all of which recovered without sequelae. No treatment-related serious adverse events occurred during the follow up of the included patients.

3.4. Clinical outcomes

Of the 6 patients who underwent the combined EBRT/MR-HIFU treatment, 5 could be followed during the complete follow up of 4 weeks after the completion of the combined treatment. In one patient, follow up had to be stopped after 14 days due worsening clinical condition as a result of abdominal primary tumor progression unrelated to the lesion in the trochanter major treated with EBRT and MR-HIFU. Decrease in pain scores was seen in all patients as early as 3 days after completed treatment. On average, pain scores decreased by 3.5 points during the 4 weeks follow up (Figs. 3 and 4). At day seven, 5 out of 6 patients (83%) experienced pain response. However, pain response in the first week may be influenced by the short course post procedural analgesic medication schedule. At three and four weeks after treatment, pain response was reported by 3 out of 5 patients (60%) (Fig. 5).

4. Discussion

The current study provides the first insights into the feasibility and safety of a combined treatment with EBRT and MR-HIFU for pain palliation of CIBP within a short time frame of maximally 4 days between the last EBRT fraction and MR-HIFU. Our results show that combining these two treatment modalities is safe and feasible and may induce rapid pain relief in the first-line treatment of CIBP. No treatment-related serious adverse effects were seen during treatment and study follow up. In the context of hospital logistics, it was possible to perform the combined treatment within 4 days in all included patients and patient tolerance of was good. Clinical outcomes were promising with pain response in 5/6 patients at 7 days after completion of the combined treatment.

Planning complex procedures in the palliative setting, where patients need to be treated as soon as possible, is challenging. The radiation oncology departments of our institutions have a one-stop-palliation practice for palliative treatments, which provides intake consultation, preparation and radiation treatment in one single day. It was crucial for us to make the combination treat-

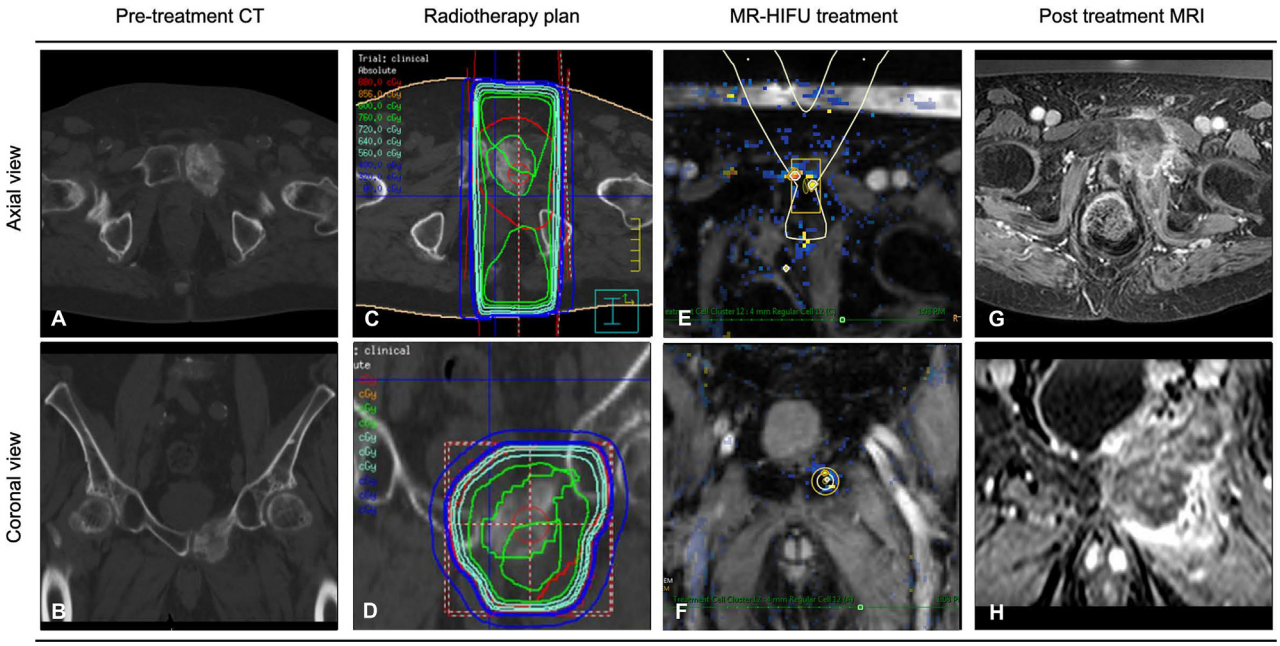

Fig. 2. Example images from treatment procedure. Example images from treatment procedure. (A + B) Pre-treatment CT-scan in axial and coronal view. Metastasis in os pubis is clearly visible. (C + D) Dosimetry plan of radiotherapy treatment on CT scan. (E + F) Screenshots of MR-thermometry during MR-HIFU treatment, showing early heating in yellow on red overlayed on anatomy. (G + H) Post treatment MRI after MR-HIFU treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

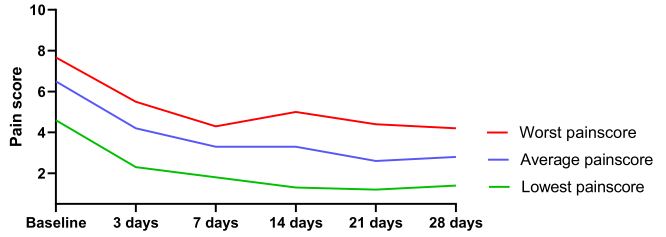

Fig. 3. Mean pain scores of all patients during follow up. Mean pain scores of all patients are given on all follow up moments on a numeric rating scale of 0–10 for their 'worst pain score' (red), 'average pain score' (blue) and 'lowest pain score' (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

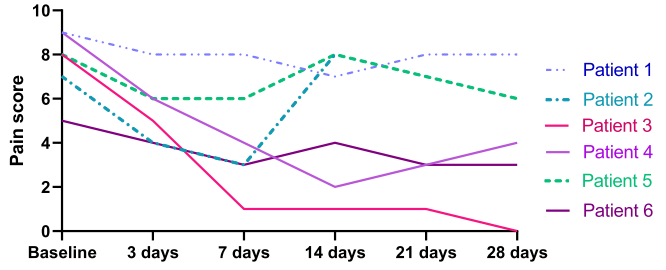

Fig. 4. Highest pain scores of individual patients during follow up. Reported 'Worst pain scores' on a numeric rating score of 0–10 during follow up. Patients 1, 2 and 5 appear to have higher overall worst scores. This may be associated with the fact that the treating interventional radiologist was not able to effectively ablate >50% of the targeted periost during the treatment time. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ment feasible within this patient-friendly practice. We achieved this by focusing on two parts of the workflow. Firstly, we allocated a weekly MR-HIFU treatment-slot for bone metastases patients. This allowed for flexible planning while still accommodating a short timeframe in between treatments. In addition,

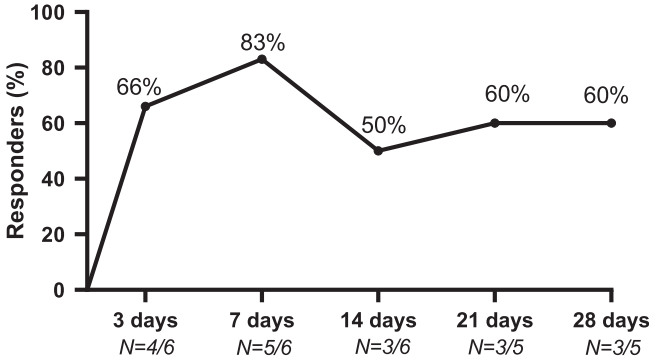

Fig. 5. Pain response during follow up. Pain response of all patients during follow up. Pain responders were defined as patients with a reduction of pain score of at least 2 points at the treated site without increase of analgesic intake, or analgesic intake reduction of at least 25% without increase of pain at the treated site. All other patients were categorized as non-responders. Note that patients received low doses of dexamethasone the first 3 days after treatment, which may have influenced pain response in the first week of follow up. Also note that one patient was lost to follow up after day 14.

post-procedural pain management and discharge on the same day was only feasible when MR-HIFU treatment took place in the morning. Close collaboration and good communication between the departments of radiation oncology and intervention radiology for rapid referral of patients turned out to be crucial for planning patients for MR-HIFU treatment within 4 days after the last EBRT fraction. At all times, radiation oncologists and intervention radiologists were available for ad hoc consultation to discuss eligibility for the combined procedure.

Although no previous research is available on the combined treatment, our results are very similar to those obtained in previous studies on MR-HIFU treatment for pain palliation treatment in patients with bone metastases. With regard to pain response previous studies reported pain responses ranging from 67% to 88% in the first month after the treatment [13,15–17,19]. We found

similar response rates with a response of 83% at 7 days after completion of the combined treatment stabilizing to 60% after 4 weeks. However, pain response in the first week may be influenced by the post procedural analgesic medication schedule. As is common practice in MR-HIFU treatment, patients received oxycodone as well as dexamethasone during 3 days after treatment, which may explain the peak of responders at 7 days after treatment. When analyzing the pain scores of individual patients, we concluded that the reduction in pain scores was stronger in patients that were treated on a later timepoint during the study. This may have several causes. Firstly, although having substantial experience with MR-HIFU treatments for other indications, the application for bone metastases was relatively new for most of our interventional radiologists. Therefore, we conclude that there is a learning-curve to be taken into account and better pain response can be expected when more experience is gained. During the study modifications on the treatment workflow and eligibility screening were made. This resulted in the inclusion of patients with a more accessible or better treatable lesion in stage IIa of the study, which may have contributed to a more successful treatment and therefore improved pain response.

The most prominent (minor) adverse event we observed in the current study was a temporary increase in pain directly after the MR-HIFU treatment in 4 of the 6 patients (66%). None of the patients experienced sonication pain during the treatment. In the study of Hurwitz et al. [13] sonication pain was seen in 32% and postprocedural pain in 4.5% of the study population. Differences in sonication pain may be due to other analgesic approaches, which ranged from local anesthesia with sedation to general anesthesia in Hurwitz's trial, and were limited to procedural sedation and analgesia in the current study. The higher percentage of post procedural pain flare in the current study may be due to a larger effect of the direct ablative process of the MR-HIFU treatment and the inflammatory reaction after radiotherapy when both modalities are combined in a short time frame. To reduce pain flare, we started prescribing a personalized three-day post procedural analgesic regimen after the first three inclusions. This regimen primarily consisted of oxycodone, dexamethasone and paracetamol the first three days after the treatment was completed. As mentioned earlier, this may also have influenced the pain response rates in the first week after treatment completion.

The biggest advantage of combining EBRT and MR-HIFU treatment could be that it achieves pain response as soon as 3 days after treatment, while also achieving the locoregional tumor control that EBRT sometimes strives for. Moreover, the combined treatment could give better results as compared to either treatment modality separately due to complimentary and possible synergistic effects in the mechanisms of action. Both radiation and ablation by heat can induce tumor specific immune responses [23–25]. A similar effect was seen when mild hyperthermia is added to radiotherapy. Although it should be noted that MR-HIFU aims for ablation at higher temperatures than hyperthermia treatment achieves, synergistic effects are likely [26]. As this study has proven that it is feasible and safe to combine EBRT and MR-HIFU. This study is the first step towards broader research on the role of MR-HIFU in the first-line treatment of CIBP. In the three-armed randomized controlled FURTHER-trial which has started enrolment in September 2020, EBRT, MR-HIFU and combined treatment will be compared (Clinical Trial registry NCT04307914).

5. Conclusion

The combined treatment of EBRT and MR-HIFU is feasible and safe in the first line of treatment of CIBP and is well tolerated by patients. Superiority over standard EBRT in terms of (time to) pain relief and quality of life need to be evaluated in the future with a comparative randomized study.

6. Data availability

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

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors declare receiving a Horizon 2020 Grant for the conduct of the submitted research. Dr. Verkooijen reports grants from Elekta, outside the submitted work.

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