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Magnetic resonance guided high-intensity focused ultrasound ablation of musculoskeletal tumors

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Abstract

This article reviews the fundamental principles and clinical experimental uses of magnetic resonance guided high-intensity focused ultrasound (MRgHIFU) ablation of musculoskeletal tumors. MRgHIFU is a noninvasive treatment modality that takes advantage of the ability of magnetic resonance to measure tissue temperature and uses this technology to guide high-intensity focused ultrasound waves to a specific focus within the human body that results in heat generation and complete thermal necrosis of the targeted tissue. Adjacent normal tissues are spared because of the accurate delivery of thermal energy, as well as, local blood perfusion that provides a cooling effect. MRgHIFU is approved by the Food and Drug Administration for the treatment of uterine fibroids and is used on an experimental basis to treat breast, prostate, liver, bone, and brain tumors.

Keywords

bone tumors; focused ultrasound; magnetic resonance thermometry; noninvasive; palliation; sarcoma

INTRODUCTION

Benign and malignant neoplasms of the musculoskeletal system are composed of a heterogeneous group of tumors originating in various tissue types including muscle, tendon, bone, cartilage, fat, and nerve. The treatment for these tumors often requires extensive surgery, and depending on the location and size of the tumor, as well as, the patient's overall medical condition, surgical treatment may lead to significant morbidity and compromise quality of life. Also, the recovery period from surgery, which may be protracted in the case of a surgical complication such as wound dehiscence or infection, may delay critical adjuvant treatments such as chemotherapy or radiotherapy. Development of noninvasive techniques that can achieve local ablation and control of tumors while minimizing complications and morbidity would be of great benefit to patients. Magnetic resonance guided high-intensity focused ultrasound (MRgHIFU) is a technology that is used to ablate

deep tissues using thermal energy generated from ultrasound waves. This technology is FDA approved for treating uterine fibroids and is used on an experimental basis to treat tumors of the liver, breast, prostate, soft tissue, and metastases to bone. This review will provide a brief overview of the technology behind MRgHIFU and its current clinical and experimental applications with respect to musculoskeletal tumors.

INTRODUCTION TO MRgHIFU

Sound travels as a pressure wave with different speeds depending on the medium through which it travels. When propagating through human tissue, the acoustic energy of the pressure wave causes tissue shearing on a microscopic level and leads to frictional heating.¹ The mechanical energy of the acoustic wave is converted to thermal energy, which is the primary mechanism behind ultrasound thermal ablation techniques.² In most circumstances, ultrasound energy travels through human tissues with very little energy deposition and no detectable rise in temperature or other harmful effects. However, when multiple acoustic pressure waves converge onto a designated focal point, sufficient energy is deposited into a focused volume to cause heating over 55°C, which leads to protein denaturation and thermal necrosis of the tissue within the focus.³ Because heating only occurs where the ultrasound waves converge, the surrounding tissue remains unaffected (Figure 1).⁴ The smaller the focus and the shorter the treatment time, which is usually under 1 minute, the more accurate is the treatment focus. Short treatment times minimize the cooling effects of local tissue blood flow, which results in a homogenous temperature rise in the target tissue and a well-defined area of ablation. When treating tumors in a clinical setting, multiple treatment foci are targeted within the tumor in an overlapping manner such that at the completion of therapy the sum of all the ablations results in complete tumor thermal necrosis (Figure 2).⁵⁻⁹

The ability to target tissues deep within the human body depends on the frequency and intensity of the ultrasound wave and the tissue properties through which the wave must travel. Lower frequency acoustic waves are better suited to penetrate deep into tissue but may require more energy to cause thermal tissue ablation while higher frequency waves cause heating more easily but tend to get absorbed more readily and therefore cannot penetrate into deep tissues.⁴ These parameters can be manipulated during high-intensity focused ultrasound treatment to maximize energy delivery to the targeted tissue. Another consideration for planning high-intensity focused ultrasound treatment is that anytime ultrasound waves travel through different mediums energy is scattered at the interface between the two mediums. Most human tissues with the exception of bone and fat have the same acoustic properties as water, for this reason liquid gel is used to couple extracorporeal ultrasound transducers to human skin. If poor coupling is achieved, the air at the interface between the ultrasound transducer and skin causes the energy to scatter; this energy is then absorbed into the surrounding area causing high temperature elevations and potential skin burn. Similarly, bone because of its density will absorb a high amount of ultrasound energy, which can lead to unwanted heating along the bone surface, while missing the target tissue. These factors must be accounted for when planning and implementing high-intensity focused ultrasound treatment.

To accurately deliver the ultrasound energy to the target volume while avoiding damage to the surrounding tissues (nerves, blood vessels, bowel loops, etc.) an accurate view of the relevant anatomy must be achieved. Historically the most common method to monitor high-intensity focused ultrasound treatments has been diagnostic ultrasound.^{10,11} This has the advantage of low cost and real time feedback on the quality of treatment. In spite of its common use, there is concern that because ultrasound does not provide thermal feedback it is not possible to accurately assess tumor cell kill. Magnetic resonance thermometry is an alternative technique to guide high-intensity focused ultrasound treatment. MRI and MR thermometry allow for accurate localization of important anatomic structures, real time temperature monitoring, and tumor ablation assessment after treatment.^{12–14} Commercially available MRgHIFU systems consist of an ultrasound apparatus that can either be built as an in-table design that fits into an MR scanner or can be built as a mobile hand held probe that can be placed on a desired anatomical location (Figure 3). Most modern high-intensity focused ultrasound machines use phased-array systems that are composed of many individual channels driving transducer elements that are individually excited by using an electronically controlled timing scheme to achieve the desired focusing of the ultrasound waves that are produced.

MRgHIFU FOR PALLIATION OF PAIN CAUSED BY BONE METASTASIS

Bone is a common organ to which cancers such as breast, prostate, lung, and many others will metastasize.¹⁵ Depending on the histology, size and location of the metastatic lesion, patients may experience severe and debilitating pain that significantly diminishes the quality of life.^{16,17} Although there are several treatment options (systemic medication, radiotherapy, surgery, and radiofrequency ablation) to help manage patients with bone metastases, these treatments are either only partially effective or have undesirable side effects.^{18–22} As a result novel treatment modalities that can alleviate symptoms while minimizing treatment related morbidity are needed.

Currently, MRgHIFU is used on a trial basis to provide palliation of pain refractory to traditional treatments in patients with bone metastasis. Most of the pain receptors in bone are believed to be located in the periosteal layer, and it is thought that treatments aimed at ablating this layer will result in lasting pain relief.²³ Bone is an ideal target for high-intensity focused ultrasound treatment because it absorbs acoustic energy up to 50 times higher than soft tissues and has a low thermal conductivity.^{24,25} As a result, nearly all of the acoustic energy of a high-intensity focused ultrasound treatment is absorbed on the surface of the bone and converted into heat that results in ablation of the surrounding periosteum. Very little energy is transmitted beyond the surface of the bone, eliminating the risk of damage to nearby tissues.²⁶ Catane *et al.*²⁷ reported 13 patients with painful bone metastases from carcinomas arising in solid organs. Eleven of these patients had lesions in the pelvic bones, one had a lesion in the humerus, and one had a lesion in the femur. The sizes of the bone lesions were not reported. Fifteen high-intensity focused ultrasound treatments were performed for 14 metastatic lesions in the 13 patients. All but one patient was able to tolerate the procedure using conscious sedation as the form of anesthesia, while one patient required an epidural. The average treatment duration was 80 minutes. There were no reported complications, although one procedure was aborted because the patient could not

tolerate the high-intensity focused ultrasound associated pain. The outcome measures were pain reported on a visual analog scale (VAS) and a self reported diary of pain medication use. The mean follow-up was 59 days. The results indicated that the pain scores and medication use had both improved; however, the extent of improvement was not quantified in the report (Figure 4). A study by Liberman *et al.*,²⁸ which expanded on the study described above and incorporated a patient group treated at Toronto General Hospital, described the results using MRgHIFU to treat 32 metastatic bone lesions in 31 patients.^{28,29} A total of 36 high-intensity focused ultrasound treatments were administered with an average treatment time of 66 minutes. Twenty-six tumors were located in the pelvic bones, two in the scapula, one each in the clavicle, femur, and humerus. The sizes of the lesions were not reported. Similar to the previous study the outcome measures were pain as measured on a VAS scale and self-reported pain medication intact. Twenty-five patients were able to complete high-intensity focused ultrasound treatment and met the 3-month minimum follow-up requirement. The authors implied that all patients had exhausted traditional palliative treatment options such as chemotherapy and radiotherapy, but the details of these treatments and their effects on outcomes were not discussed. In this group of patients the average pre-treatment VAS pain score was 5.9 (range 3.5–8.5), which improved to an average score of 3.8 (range 0–8.5) 3 days after treatment but did not meet statistical significance. However, at 3 months after treatment the average VAS pain score improved to 1.8 (range 0–8), which was statistically significant when compared to 3 days after treatment. Nineteen of the 25 patients reported a decrease in pain medication use while two patients increased the use of pain medication. Overall, 36% of patients had a complete response to treatment defined as a pain score of 0 with no concomitant increase in pain medication, 36% had a partial response defined as a drop in pain score of at least two with no increase in pain medication or no change in pain score but at least a 25% reduction in pain medication intake, 24% had no response to treatment, and 4% had pain progression.

These studies suggest that there is a role for MRgHIFU in palliating pain from bone metastasis especially in cases involving the pelvis, sacrum, and scapula, where surgical intervention may be difficult. Some potential advantages to using high-intensity focused ultrasound in this clinical setting are that most patients improve after only a single treatment. High-intensity focused ultrasound does not have side effects associated with ionizing radiation, and there is no limit to the number of treatments a patient can receive. Also, high-intensity focused ultrasound treatments can be used safely as an adjunct to or concomitantly with other treatments such as chemotherapy, surgery and radiotherapy. In spite of these advantages, however, there are several limitations to high-intensity focused ultrasound that must be considered when treating patients. Important clinical factors when dealing with bone metastasis are the size and location of a given lesion. Neither of the studies referenced above detailed the size of the lesions; however, given that the average baseline VAS pain score was 5.9, which at least in our practice is a relatively low pain level, one would presume the lesions were relatively small. This is important because the treatment volume of a single high-intensity focused ultrasound is approximately only 1 cm³ in soft tissues albeit somewhat larger on bone surfaces. To treat larger tumors a higher number of high-intensity focused ultrasound sonications may be necessary, making the treatment sessions time consuming. Fortunately, owing to its high absorption coefficient, treating bone is not limited

to small focal points and therefore is much more rapid than treating soft tissues. Also, in spite of alleviating pain by destroying the pain receptors in the periosteum, the high-intensity focused ultrasound acoustic beams may not be able to penetrate through the bone deep enough to cause definitive tumor ablation. Therefore, the tumor, if left untreated, may eventually progress and cause further bone destruction and possible mechanical instability or fracture. Finally, any metastasis to the appendicular skeleton that places the bone at risk for pathologic fracture likely would not be a candidate for high-intensity focused ultrasound as a single mode of treatment. Current research is being conducted to address these issues.

TREATMENT OF PRIMARY BONE TUMORS

Primary bone tumors are difficult to treat with MRgHIFU because most ultrasound energy is absorbed by the cortex of the bone, which essentially shields the medullary canal from the acoustic wave. Since most bone sarcomas are located inside the intramedullary space a typical high-intensity focused ultrasound treatment would not be effective. However, in many cases the sarcoma breaks out of the intramedullary space and forms a soft-tissue mass. If there is a large enough break in the bone cortex then this space may be used as an acoustic window to allow penetration of the high-intensity focused ultrasound energy into the intramedullary space and effectively ablate the tumor.

A recent study from China examined the effectiveness of ultrasound-guided high-intensity focused ultrasound for treating primary bone sarcomas. Li *et al.*³⁰ reported 13 patients with primary bone tumors (12 osteosarcomas and one malignant fibrous histiocytoma of bone). Inclusion criteria into the study or information on why these patients did not undergo gold standard treatment with surgical resection were not provided. The mean age of these patients was 32.9 years (range 9–65 years). Staging information was not provided nor was the intracompartmental or extracompartmental status of the tumor indicated; however, the average longest dimension of the tumors was 9.8 cm (range 6–16). High-intensity focused ultrasound treatments were performed under general anesthesia. The high-intensity focused ultrasound treatments were delivered to the entire tumor with an additional 2-cm margin of normal soft tissue and 2–3-cm margin of additional bone tissue. Outcome measures included pain level, serum alkaline phosphatase and lactate dehydrogenase levels, and radiographic evaluation of high-intensity focused ultrasound induced tumor necrosis based on MRI or PET-CT. The specifics on which patients received MRI or PET-CT were not reported. The radiographic response was measured based on World Health Organization criteria with (1) complete response (CR) being whole tumor necrosis for more than 4 weeks; (2) partial response (PR), tumor necrosis of more than 50% or 50% decrease in volume for more than 4 weeks; (3) moderate response (MR), necrosis of more than 50% or 25% size decrease; (4) stable disease (SD), an increase or decrease in the size of the tumor by less than 25%; (5) progressive disease (PD). Finally survival data were presented as Kaplan-Meier curves; however, the time of actual follow-up was not reported.

The results indicated that all patients had improvement in pain and serum alkaline phosphate and lactate dehydrogenase levels. Six patients had a CR, five had PR, one had MR, and one had PD. The median overall survival was 43.0 months. Kaplan-Meier survival estimates were approximately 40% at 60 months and 10% at 80 months. There was no discussion on

local control rate. The authors concluded that high-intensity focused ultrasound was a safe and effective treatment modality for osteosarcoma.

Although the information presented in this study is intriguing, caution must be used when interpreting the results. The stage of disease was not presented nor was the rationale for not offering patients an opportunity for surgical resection of disease, which is known to be the single most important variable for long-term survival.^{31–38} The outcome measure of MRI and PET-CT as the definitive evaluation of tumor necrosis is problematic at best. Although these imaging tools are useful in estimating tumor necrosis and surgical planning, they lack the resolution to determine if complete tumor ablation has occurred. One report estimated contrast-enhanced MRI's ability to detect tumor down to 2 mm², which is a arguably a good resolution; however, much less tumor than 1 mm² is sufficient to cause local recurrence and subsequent metastasis.^{35,39–41} Also, in the current study there was no mention of the local control rate, which seems to be a significant omission given that the goal of high-intensity focused ultrasound is to achieve local control of primary bone sarcomas, and the reader does not know if this has been achieved. Lastly, the length of follow-up was not specified; however, the overall survival was estimated to be approximately 40% which is less than 50–60% survival at 5 years expected with modern chemotherapy and surgery for patients presenting with localized disease. This technique should not be used as a primary treatment modality for primary bone sarcomas outside of an ethics committee approved clinical trial.

TREATMENT OF SOFT-TISSUE TUMORS OF THE EXTREMITIES

High-intensity focused ultrasound has been used to treat many types of solid tumors; however, there are no reported series describing its use on soft-tissue tumors of the extremities. At our institution we are developing a research program to investigate the use of MRgHIFU for this clinical application. Preliminary studies performed in our lab using the Exablate 2000 high-intensity focused ultrasound system (InSightec, Haifa, Israel) integrated into a 3 T GE Signa whole body MR scanner demonstrated the feasibility of using MRgHIFU to ablate extremity tumors (Figure 5). We did, however, identify several items that need to be improved in order to maximize safety and efficacy of MRgHIFU before treating human patients in the clinical setting. Examples include: how to safely couple the transducer to different anatomic locations on the extremity, determining how close high-intensity focused ultrasound system can be administered to major peripheral nerves and vascular structures, determining how to best perform MR thermometry on adipose tissue, determining the effect of ablating tumors through thick collagen bands such as the Achilles tendon. These experiments will be conducted in the coming months.

CONCLUSION

MRgHIFU is a noninvasive treatment modality that uses magnetic resonance thermometry to guide the delivery of high-intensity ultrasound waves to a specific focus within the human body causing thermal necrosis of the targeted tissue while sparing the adjacent anatomy. The technical considerations and feasibility of MRgHIFU depends on the types of tumors being ablated and factors related to their anatomical location such as proximity to major nerves, arteries, bowel loops, etc. To date this treatment modality is FDA-approved for the treatment

of uterine fibroids and is used on an experimental basis to treat breast, prostate, liver, bone, and brain tumors. Orthopaedic application of this technology is experimental and literature on this topic is limited. Further research is necessary to determine MRgHIFU's role in each of these clinical applications.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Wood R, Loomis A. The physical and biological effects of high frequency sound waves of greater intensity. *Dublin Philos Mag J Sci.* 1927; 4:417–436.
2. Lynn JG, Zwemer RL, Chick AJ, et al. A new method for the generation and use of focused ultrasound in experimental biology. *J Gen Physiol.* 1942; 26:179–193. [PubMed: 19873337]
3. Linke CA, Carstensen EL, Frizzell LA, et al. Localized tissue destruction by high-intensity focused ultrasound. *Arch Surg.* 1973; 107:887–891. [PubMed: 4751833]
4. Haar GT, Coussios C. High intensity focused ultrasound: physical principles and devices. *Int J Hyperthermia.* 2007; 23:89–104. [PubMed: 17578335]
5. Wu F, Wang ZB, Cao YD, et al. “Wide local ablation” of localized breast cancer using high intensity focused ultrasound. *J Surg Oncol.* 2007; 96:130–136. [PubMed: 17443737]
6. Chan AH, Fujimoto VY, Moore DE, et al. An image-guided high intensity focused ultrasound device for uterine fibroids treatment. *Med Phys.* 2002; 29:2611–2620. [PubMed: 12462728]
7. Ren XL, Zhou XD, Zhang J, et al. Extracorporeal ablation of uterine fibroids with high-intensity focused ultrasound: imaging and histopathologic evaluation. *J Ultrasound Med.* 2007; 26:201–212. [PubMed: 17255182]
8. Mahajan NN, Gaikwad NL, Soni RN, et al. Extracorporeal ablation of uterine fibroids with high-intensity focused ultrasound. *J Ultrasound Med.* 2007; 26:702. [PubMed: 17460017]
9. ter Haar G, Sinnett D, Rivens I. High intensity focused ultrasound—a surgical technique for the treatment of discrete liver tumours. *Phys Med Biol.* 1989; 34:1743–1750. [PubMed: 2685839]
10. Yang R, Reilly CR, Rescorla FJ, et al. Effects of high-intensity focused ultrasound in the treatment of experimental neuroblastoma. *J Pediatr Surg.* 1992; 27:246–250. discussion 250–251. [PubMed: 1564625]
11. Ren XL, Zhou XD, Yan RL, et al. Sonographically guided extracorporeal ablation of uterine fibroids with high-intensity focused ultrasound: midterm results. *J Ultrasound Med.* 2009; 28:100–103. [PubMed: 19106367]
12. Jacobs MA, Gultekin DH, Kim HS. Comparison between diffusion-weighted imaging, T2-weighted, and postcontrast T1-weighted imaging after MR-guided, high intensity, focused ultrasound treatment of uterine leiomyomata: preliminary results. *Med Phys.* 2010; 37:4768–4776. [PubMed: 20964196]
13. Ram Z, Cohen ZR, Harnof S, et al. Magnetic resonance imaging-guided, high-intensity focused ultrasound for brain tumor therapy. *Neurosurgery.* 2006; 59:949–955. discussion 955–956. [PubMed: 17143231]
14. Hynynen K, Damianou C, Darkazanli A, et al. The feasibility of using MRI to monitor and guide noninvasive ultrasound surgery. *Ultrasound Med Biol.* 1993; 19:91–92. [PubMed: 8456533]
15. Weber KL, Randall RL, Grossman S, et al. Management of lower-extremity bone metastasis. *J Bone Joint Surg.* 2006; 88-A(suppl 4):11–19. [PubMed: 17142431]
16. Coleman RE, Lipton A, Roodman GD, et al. Metastasis and bone loss: advancing treatment and prevention. *Cancer Treat Rev.* 2010; 36:615–620. [PubMed: 20478658]

17. Yoneda T, Sasaki A, Mundy GR. Osteolytic bone metastasis in breast cancer. *Breast Cancer Res Treat.* 1994; 32:73–84. [PubMed: 7819589]
18. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol.* 2007; 25:1423–1436. [PubMed: 17416863]
19. Kohno N. Treatment of breast cancer with bone metastasis: bisphosphonate treatment-current and future. *Int J Clin Oncol.* 2008; 13:18–23. [PubMed: 18307015]
20. Raffaelli L, Scaramuzzo L, Rossi Iommetti P, et al. Jaw osteonecrosis related to bisphosphonate treatment of bone metastasis. *J Biol Regul Homeost Agents.* 2010; 24:115–121. [PubMed: 20487624]
21. Altundag O, Altundag K, Selim Silay Y, et al. Calcium and vitamin D supplementation during bisphosphonate administration may increase osteoclastic activity in patients with bone metastasis. *Med Hypotheses.* 2004; 63:1010–1013. [PubMed: 15504568]
22. Goetz MP, Callstrom MR, Charboneau JW, et al. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *J Clin Oncol.* 2004; 22:300–306. [PubMed: 14722039]
23. Bennett A. The role of biochemical mediators in peripheral nociception and bone pain. *Cancer Surv.* 1988; 7:55–67. [PubMed: 2898291]
24. Smith NB, Temkin JM, Shapiro F, et al. Thermal effects of focused ultrasound energy on bone tissue. *Ultrasound Med Biol.* 2001; 27:1427–1433. [PubMed: 11731056]
25. Zimmerman MC, Prabhakar A, Chokshi BV, et al. The acoustic properties of normal and imbedded bovine bone as measured by acoustic microscopy. *J Biomed Mater Res.* 1994; 28:931–938. [PubMed: 7983091]
26. Bensamoun S, Ho Ba Tho MC, Luu S, et al. Spatial distribution of acoustic and elastic properties of human femoral cortical bone. *J Biomech.* 2004; 37:503–510. [PubMed: 14996562]
27. Catane R, Beck A, Inbar Y, et al. MR-guided focused ultrasound surgery (MRgFUS) for the palliation of pain in patients with bone metastases-preliminary clinical experience. *Ann Oncol.* 2007; 18:163–167. [PubMed: 17030549]
- 28•. Liberman B, Gianfelice D, Inbar Y, et al. Pain palliation in patients with bone metastases using MR-guided focused ultrasound surgery: a multicenter study. *Ann Surg Oncol.* 2009; 16:140–146. Thirty-one patients with painful metastatic bone tumors were treated with HIFU for palliation of pain. There was improvement in visual analog pain score. [PubMed: 19002530]
29. Gianfelice D, Gupta C, Kucharczyk W, et al. Palliative treatment of painful bone metastases with MR imaging—guided focused ultrasound. *Radiology.* 2008; 249:355–363. [PubMed: 18695209]
30. Li C, Zhang W, Fan W, et al. Noninvasive treatment of malignant bone tumors using high-intensity focused ultrasound. *Cancer.* 2010; 116:3934–3942. [PubMed: 20564113]
31. Bielack SS, Kempf-Bielack B, Winkler K. Osteosarcoma: relationship of response to preoperative chemotherapy and type of surgery to local recurrence. *J Clin Oncol.* 1996; 14:683–684. [PubMed: 8636791]
32. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol.* 2002; 20:776–790. [PubMed: 11821461]
33. Sluga M, Windhager R, Lang S, et al. Local and systemic control after ablative and limb sparing surgery in patients with osteosarcoma. *Clin Orthop Relat Res.* 1999; 358:120–127. [PubMed: 9973983]
34. Picci P, Sangiorgi L, Rougraff BT, et al. Relationship of chemotherapy-induced necrosis and surgical margins to local recurrence in osteosarcoma. *J Clin Oncol.* 1994; 12:2699–2705. [PubMed: 7989947]
35. Ferrari S, Bertoni F, Mercuri M, et al. Predictive factors of disease-free survival for non-metastatic osteosarcoma of the extremity: an analysis of 300 patients treated at the Rizzoli Institute. *Ann Oncol.* 2001; 12:1145–1150. [PubMed: 11583198]
36. Bacci G, Longhi A, Briccoli A, et al. The role of surgical margins in treatment of Ewing's sarcoma family tumors: experience of a single institution with 512 patients treated with adjuvant and neoadjuvant chemotherapy. *Int J Radiat Oncol Biol Phys.* 2006; 65:766–772. [PubMed: 16626886]

37. Bacci G, Longhi A, Cesari M, et al. Influence of local recurrence on survival in patients with extremity osteosarcoma treated with neoadjuvant chemotherapy: the experience of a single institution with 44 patients. *Cancer*. 2006; 106:2701–2706. [PubMed: 16691623]
38. Jaffe N, Carrasco H, Raymond K, et al. Can cure in patients with osteosarcoma be achieved exclusively with chemotherapy and abrogation of surgery? *Cancer*. 2002; 95:2202–2210. [PubMed: 12412175]
39. van der Woude HJ, Bloem JL, Verstraete KL, et al. Osteosarcoma and Ewing's sarcoma after neoadjuvant chemotherapy: value of dynamic MR imaging in detecting viable tumor before surgery. *AJR Am J Roentgenol*. 1995; 165:593–598. [PubMed: 7645476]
40. Brisse H, Ollivier L, Edeline V, et al. Imaging of malignant tumours of the long bones in children: monitoring response to neoadjuvant chemotherapy and preoperative assessment. *Pediatr Radiol*. 2004; 34:595–605. [PubMed: 15103428]
41. Holscher HC, Bloem JL, Vanel D, et al. Osteosarcoma: chemotherapy-induced changes at MR imaging. *Radiology*. 1992; 182:839–844. [PubMed: 1535905]

FIGURE 1.

Diagrammatic illustration of the principle of high-intensity focused ultrasound (HIFU). High-intensity ultrasound waves are generated by a transducer outside the body and focused onto to a small region deep within tissue. HIFU-induced heating causes cell death by thermal necrosis within the focal volume, but leaves tissue elsewhere in the propagation path unaffected. Adapted from Haar GT, Coussios C. High Intensity Focused Ultrasound: Physical Principles and Devices. *Int J Hyperthermia*. 2007.

FIGURE 2.

Diagrammatic illustration of high-intensity focused ultrasound treatment delivery for the ablation of large tissue volumes. Multiple lesions are created side-by-side to span the required treatment volume, starting on the side distal to the transducer. The lesions can be overlapping or separate, depending on the necessity to achieve confluent regions of cell killing. Adapted from Haar GT, Coussios C. High Intensity Focused Ultrasound: Physical Principles and Devices. *Int J Hyperthermia*. 2007.

FIGURE 3.

(A) The ExAblate 2000 (InSightec, Haifa, Israel) system is an FDA-approved device for the treatment of uterine fibroids. The transducer is built into the MR table, within an oil bath, and the patient lies above it, coupled with a gel pad and degassed water. The transducer is on a four-axis positioning system and is capable of tilting to access difficult targets, and is also capable of on-axis steering. It is a piezoelectric transducer (PZT) composite sector vortex array with a diameter of 120 mm and a radius of curvature of 160 mm. The array has a bandwidth of 0.9 MHz–1.35 MHz and is about 50% efficient. (B) The InSightec bone system (InSightec, Haifa, Israel) is a movable phased array transducer. It is designed to be strapped onto the patient at the point of access to painful bone metastases. It is comprised of a two-dimensional, flat, square transducer with 1024 PZT elements. It is 80 mm × 80 mm with a center frequency of 0.55 MHz and is about 50% efficient. A membrane on the surface of the transducer holds degassed water used for coupling to the patient. (www.insightec.com).

FIGURE 4.

Average visual analog scale score of 13 patients (15 treatments) during follow-up.

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FIGURE 5.

MR guided high-intensity focused ultrasound (HIFU) ablation in a cadaver lower leg. (A) Axial T1 MR image of a human cadaver lower leg undergoing HIFU planning. The yellow cylinders represent planned areas of sonication, in this case where the rice noodles were placed as fiducials. The blue hourglass represents the trajectory of the ultrasound energy with the focus located at the waist. (B) Coronal T1 MR image. The yellow circles represent the coronal view appearance of the same areas to be sonicated. (C) Coronal T1-weighted image of the area treated (blue) by MR thermometry. (D) Tissue specimen showing treated area.