

# **Compendium of *Focused Ultrasound* Clinical Publications**

This compendium includes papers describing clinical experience gathered on **Ultrasound Guided systems (in dark blue)** and MR Guided systems (in Black) by multiple vendors. Papers in each section are ordered by date.

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## **I. Reviews**

Hynynen K. *MRI-guided Focused Ultrasound Treatments*, Ultrasonics, 2009.

Focused ultrasound (FUS) allows noninvasive focal delivery of energy deep into soft tissues. The focused energy can be used to modify and eliminate tissue for therapeutic purposes while the energy delivery is targeted and monitored using magnetic resonance imaging (MRI). MRI compatible methods to deliver these exposures have undergone rapid development over the past 10 years such that clinical treatments are now routinely performed. This paper will review the current technical and clinical status of MRI-guided focused ultrasound therapy and discuss future research and development opportunities.

**[MR Guided]**

Jolesz FA. *MRI-Guided Focused Ultrasound Surgery*, Annu.Rev.Med., 2009, 60:417-30.

MRI-guided focused ultrasound (MRgFUS) surgery is a noninvasive thermal ablation method that uses magnetic resonance imaging (MRI) for target definition, treatment planning, and closed-loop control of energy deposition. Integrating FUS and MRI as a therapy delivery system allows us to localize, target, and monitor in real time, and thus to ablate targeted tissue without damaging normal structures. This precision makes MRgFUS an attractive alternative to surgical resection or radiation therapy of benign and malignant tumors. Already approved for the treatment of uterine fibroids, MRgFUS is in ongoing clinical trials for the treatment of breast, liver, prostate, and brain cancer and for the palliation of pain in bone metastasis. In addition to thermal ablation, FUS, with or without the use of microbubbles, can temporarily change vascular or cell membrane permeability and release or activate various compounds for targeted drug delivery or gene therapy. A disruptive technology, MRgFUS provides new therapeutic approaches and may cause major changes in patient management and several medical disciplines.

**[MR Guided]**

Bradley WG Jr., **MR-guided focused ultrasound: a potentially disruptive technology.** J Am Coll Radiol. 2009 Jul;6(7):510-3.

A disruptive technology is a technological innovation that overturns the existing dominant technologies in a market. Magnetic resonance (MR)-guided focused ultrasound (MRgFUS) is a noninvasive procedure based on the combination of real-time MR anatomic guidance, MR thermometry, and high-intensity focused ultrasound. Several hundred transducer elements become convergent at a point under MR guidance, leading to heating and coagulation necrosis. Outside the focal point, there is no significant heating. There is no need to break the skin for procedures in the body or to perform a craniotomy for procedures in the brain. This lack of invasiveness is what makes MRgFUS so disruptive compared with surgery. At present, MRgFUS has been used for the ablation of uterine fibroids, breast tumors, painful bony metastases, and liver tumors. In the brain, it has been used for the ablation of glioblastomas and for functional neurosurgery. Phantom and animal studies suggest future applications for prostate cancer and acute stroke treatment.

**[MR Guided]**

Ferenc A. Jolesz (Editor), Kullervo H. Hynynen (Editor), ***MRI-Guided Focused Ultrasound Surgery***

~ MRI-Guided Focused Ultrasound Surgery is the first book on this new technology, and it presents a variety of current and future clinical applications in tumor ablation treatment. This source helps surgeons and specialists evaluate, analyze, and utilize MRI-guided focused ultrasound surgery - bridging the gap between phase 3 clinical trials and the expansion to the clinical practice - by exploring fundamental principles and future clinical applications using this new therapeutic method.

**[BOOK]**

## **II. Uterine Fibroids**

Fennessy FM, Tempany CM, McDannold NJ, So MJ, Hesley G, Gostout B, Kim HS, Holland GA, Sarti DA, Hynynen K, Jolesz FA, Stewart EA. ***Uterine leiomyomas: MR imaging-guided focused ultrasound surgery--results of different treatment protocols.*** Radiology. 2007 Jun;243(3):885-93.

**PURPOSE:** To prospectively assess patient response (after 12 months) to magnetic resonance (MR) imaging-guided focused ultrasound surgery in treatment of uterine leiomyomas by using two treatment protocols.

**MATERIALS AND METHODS:** This prospective clinical trial was approved by institutional review boards and was HIPAA compliant. After giving informed consent, patients with symptomatic leiomyomas were consecutively enrolled and treated at one of five U.S. centers by using an original or a modified protocol. Outcomes were assessed with the symptom severity score (SSS) obtained at baseline and 3, 6, and 12 months after treatment. Adverse events (AEs) were recorded. Statistical analysis included Student t test, Fisher exact test, analysis of covariance, Spearman correlation, and logistic regression.

**RESULTS:** One hundred sixty patients had a mean SSS of 62.1 +/- 16.3 (standard deviation) at baseline, which decreased to 35.5 +/- 19.5 at 3 months ( $P < .001$ ) and to 32.3 +/- 19.8 at 6 months ( $P < .001$ ) and was 32.7 +/- 21.0 at 12 months ( $P < .001$ ). Ninety-six patients (mean age, 46.0 years +/- 4.6) were treated with an original protocol, and 64 (mean age, 45.9 years +/- 3.9) were treated with a modified protocol. Patients in the modified group had a significantly greater SSS decrease at 3 months ( $P = .037$ ) than those in the original group, and 73% of those in the original group and 91% of those in the modified group reported a significant decrease in SSS (of 10 points or greater) at 12 months. No serious AEs were recorded. Fewer AEs were reported in the modified group than in the original group (25% vs 13% reporting no event). Of evaluable patients, fewer in the modified group chose alternative treatment (28%) than in the original group (37%).

**[MR Guided]**

Stewart E, Gostout B, Rabinovici J, Kim HS, Regan L, Tempany CM for the MRI guided Focused Ultrasound for Uterine Fibroid Group. ***Sustained Relief of Leiomyoma Symptoms by Using Focused Ultrasound Surgery***, Obstetrics & Gynecology, 2007, 110(2):279-287.

**OBJECTIVE:**

To assess several measures of the long-term outcome of magnetic resonance-guided focused ultrasound surgery for symptomatic uterine leiomyomata.

**METHODS:**

Data on 359 women completing 24-month follow-up in all clinical trials of magnetic resonance-guided focused ultrasound surgery for uterine leiomyomata were analyzed. Quality of life outcomes, measured by the symptom severity score of the Uterine Fibroid Symptoms Quality Of Life Questionnaire were assessed for 24 months after treatment. Clinical endpoints, including uterine shrinkage, the need for additional leiomyoma treatment, and the time to additional leiomyoma treatment, were all assessed. The nonperfused volume ratio after treatment, calculated from the gadolinium-enhanced magnetic resonance imaging after treatment and the best measure of tissue necrosis after treatment, was used to assess outcome based on completeness of leiomyoma ablation.

**RESULTS:**

Women undergoing magnetic resonance-guided focused ultrasound surgery for symptomatic uterine leiomyomata have durable symptom relief, as measured by the symptom severity score at 24 months, with significantly greater improvement with more complete ablation ( $P < .001$ ). Survival analysis demonstrates a significant reduction in the percentage of women undergoing additional leiomyoma treatment ( $P = .001$ ) in women in the high nonperfused volume group. The mean shrinkage and mean residual nonperfused volume ratio are both significantly above zero at 6 months in the high nonperfused volume group ( $P < .001$ ). The incidence of adverse events is low. However, for women with minimal treatment, the risk of additional procedures is high.

**CONCLUSION:** Magnetic resonance-guided focused ultrasound surgery is an effective treatment for uterine leiomyomata and results in sustained symptomatic relief.

**[MR Guided]**

Zowall H, Cairns JA, Brewer C, Lamping DL, Gedroyc WM, Regan L. **Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids.** BJOG. 2008 Apr;115(5):653-62.

**OBJECTIVE:** To estimate the cost-effectiveness of a treatment strategy for symptomatic uterine fibroids, which starts with Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) as compared with current practice comprising uterine artery embolisation, myomectomy and hysterectomy.

**DESIGN:** Cost-utility analysis based on a Markov model.

**SETTING:** National Health Service (NHS) Trusts in England and Wales.

**POPULATION:** Women for whom surgical treatment for uterine fibroids is being considered.

**METHODS:** The parameters of the Markov model of the treatment of uterine fibroids are drawn from a series of clinical studies of MRgFUS, and from the clinical effectiveness literature. Health-related quality of life is measured using the 6D. Costs are estimated from the perspective of the NHS. The impact of uncertainty is examined using deterministic and probabilistic sensitivity analysis.

**MAIN OUTCOME MEASURES:** Incremental cost-effectiveness measured by cost per quality-adjusted life-year (QALY) gained.

**RESULTS:** The base-case results imply a cost saving and a small QALY gain per woman as a result of an MRgFUS treatment strategy. The cost per QALY gained is sensitive to cost of MRgFUS relative to other treatments, the age of the woman and the nonperfused volume relative to the total fibroids volume.

**CONCLUSIONS:** A treatment strategy for symptomatic uterine fibroids starting with MRgFUS is likely to be cost-effective.

**[MR Guided]**

Rabinovici J, David M, Fukunishi M, Morita Stewart E, "*MR guided Focused Ultrasound Pregnancies: Pregnancy outcome following magnetic resonance guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids.*" Fertility and Sterility, 2008 Nov 13.

**OBJECTIVE:** To report all pregnancies to date after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for the conservative treatment of clinically significant uterine fibroids.

**DESIGN:** Prospective registry of all known pregnancies occurring after MRgFUS maintained by the device manufacturer and reported to the Food and Drug Administration.

**SETTING:** World experience of pregnancies after treatment with reports from 13 sites in seven countries.

**PATIENT(S):** Fifty-one reproductive-age women with uterine leiomyomas.

**INTERVENTION(S):** Women underwent MRgFUS treatment for symptomatic uterine leiomyomas before this report.

**MAIN OUTCOME MEASURE(S):** Pregnancy outcomes and complications.

**RESULT(S):** Fifty-four pregnancies in 51 women have occurred after MRgFUS treatment of uterine leiomyomas. The mean time to conception was 8 months after treatment. Live births occurred in 41% of pregnancies, with a 28% spontaneous abortion rate, an 11% rate of elective pregnancy termination, and 11 (20%) ongoing pregnancies beyond 20 gestational weeks. The mean birth weight was 3.3 kg, and the vaginal delivery rate was 64%.

**CONCLUSION(S):** Preliminary pregnancy experience after MRgFUS is encouraging, with a high rate of delivered and ongoing pregnancies.

**[MR Guided]**

Okada A, Morita Y, Fukunishi H, Takeichi K, Murakami T. ***Non-invasive Magnetic Resonance-guided Focused Ultrasound Treatment of Uterine Fibroids in a Large Japanese Population: Impact of the Learning Curve on Patient Outcome***, *Ultrasound Obstet Gynecol*, 2009, 34:579-583.

**OBJECTIVES:** To describe the learning curve effect of magnetic resonance-guided focused ultrasound surgery (MRgFUS) on the outcomes of patients treated for uterine fibroids in four centers in Japan.

**METHODS:** The extent of fibroid ablation (often used to measure treatment success) was evaluated using the non-perfused volume (NPV) ratio in 287 Japanese patients. The patients were divided into two equal groups according to the chronological treatment time and results were compared between these groups to estimate the learning curve effect. Results were also compared with published data from clinical trials.

**RESULTS:** The NPV ratio increased chronologically, from 39.3% to 54.0% ( $P < 0.001$ ), indicating increasing effectiveness of the treatment with experience. The mean NPV ratios for the entire patient population were over double that of previous clinical trials (46.6% vs. 21.9%;  $P < 0.001$ ). No serious complications were reported.

**CONCLUSION:** The learning process and accumulation of data on MRgFUS enable the optimization of treatments in order to safely achieve large NPV ratios and sustained clinical benefit.

**[MR Guided]**

Taran FA, Tempany CMC, Regan L, Inbar Y, Revel A, Stewart EA. ***Magnetic Resonance-guided Focused Ultrasound (MRgFUS) Compared with Abdominal Hysterectomy for Treatment of Uterine Leiomyomas***, *Ultrasound Obstet Gynecol*, 2009, 34:572-578.

**OBJECTIVES:** To compare women undergoing magnetic resonance-guided focused ultrasound (MRgFUS) to a group of contemporaneously recruited women undergoing total abdominal hysterectomy. Patient demographics, safety parameters, quality of life outcomes and disability measures are reported.

**METHODS:** One hundred and nine women were recruited in seven centers for MRgFUS treatment and 83 women who underwent abdominal hysterectomy were recruited in seven separate centers to provide contemporaneous assessment of safety. The adverse-event profile and disability parameters were prospectively assessed. Patients were also screened at baseline and at 1, 3 and 6 months using the SF-36 health survey questionnaire.

**RESULTS:** There were no life-threatening adverse events in either group. Overall, the number of significant clinical complications and adverse events was lower in women in the MRgFUS group compared to women undergoing hysterectomy. MRgFUS was associated with significantly faster recovery, including resumption of usual activities. At 6 months of follow-up, there were four (4%) treatment failures in the MRgFUS arm. Regarding SF-36 subscale scores, at 6 months there was improvement in all SF-36 subscales for both treatment groups. However, most of the SF-36 subscale scores were significantly better at this stage in the hysterectomy group than in the MRgFUS group. Women undergoing MRgFUS had steady improvement in all parameters throughout the 6-month follow-up period, despite the fact that they continued to have myomatous uteri and menstruation, which at baseline had given them significant symptomatology.

**CONCLUSIONS:** The results of this study show that MRgFUS treatment of uterine leiomyomas leads to clinical improvement with fewer significant clinical complications and adverse events compared to hysterectomy at 6 months' follow-up.

**[MR Guided]**

O'Sullivan AK, Thompson D, Chu P, Lee DW, Stewart EA, Weinstein MC. **Cost-effectiveness of Magnetic Resonance guided Focused Ultrasound for the Treatment of Uterine Fibroids**, International Journal of Technology Assessment in Health, 2009, 25(1):14-25.

**OBJECTIVES:** The aim of this study is to evaluate the cost-effectiveness of Magnetic Resonance Guided Focused Ultrasound (MRgFUS) compared with alternative treatments for uterine fibroids in the United States.

**METHODS:** We used techniques of decision analysis and data from secondary sources to develop and estimate an economic model of the management of uterine fibroids among premenopausal women. Patients in the model receive treatment with MRgFUS, uterine artery embolization (UAE), abdominal myomectomy, hysterectomy, or pharmacotherapy. The model predicts total costs (including subsequent procedures) and quality-adjusted life-years (QALYs) for each treatment strategy over a lifetime horizon, discounted at 3 percent, from a societal perspective. Data on treatment efficacy and safety were obtained from published and unpublished studies. Costs (2005 US\$) were obtained from an analysis of a large administrative database and other secondary sources. Lost productivity costs were included in the base-case analysis, but excluded in a sensitivity analysis.

**RESULTS:** UAE was associated with the most QALYs (17.39), followed by MRgFUS (17.36), myomectomy (17.31), hysterectomy (17.18), and pharmacotherapy (16.70). Pharmacotherapy was the least costly strategy (\$9,200 per patient), followed by hysterectomy (\$19,800), MRgFUS (\$27,300), UAE (\$28,900), and myomectomy (\$35,100). Incremental cost-effectiveness ratios (cost per QALY gained) were \$21,800 for hysterectomy, \$41,400 for MRgFUS, and \$54,200 for UAE; myomectomy was more costly and less effective than both MRgFUS and UAE. Results were sensitive to MRgFUS recurrence rates, MRgFUS procedure costs, and assumptions about quality of life following hysterectomy.

**CONCLUSIONS:** Our findings suggest that MRgFUS is in the range of currently accepted criteria for cost-effectiveness, along with hysterectomy and UAE.

**[MR Guided]**

Funaki K, Fukunishi H, Sawada K., ***Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up***, *Ultrasound Obstet Gynecol.* 2009 Nov;34(5):584-9.

**OBJECTIVES:** To assess the volume reduction ratio, symptom improvement and reintervention rate following magnetic resonance-guided focused ultrasound surgery (MRgFUS) for uterine myomas.

**METHODS:** A total of 91 Japanese women with symptomatic myomas underwent MRgFUS between June 2004 and June 2008 using the ExAblate 2000 system. The volume change ratio was calculated at 6, 12 and 24 months following MRgFUS based on T2-weighted magnetic resonance images. The symptom severity score (SSS) was examined before and after the treatment (at 3, 6, 12 and 24 months). Additional post-MRgFUS treatments, such as hysterectomy, myomectomy, uterine artery embolization or repeat MRgFUS, were recorded and the reinterventional treatment rates were compared according to the signal intensity of pretreatment T2-weighted magnetic resonance images of the myomas.

**RESULTS:** The mean volume change ratios of low- and intermediate-intensity (Type 1/2) myomas were -36.5% 6 months post-procedure and -39.5% 24 months post-procedure. The mean +/- SD SSS value for patients with Type 1/2 myomas before MRgFUS was 35.1 +/- 21.0, and the values diminished significantly during the 24-month follow-up period to a mean value of around 15.0. High-intensity (Type 3) myomas were not observed to have decreased in size 6 months after MRgFUS. Of the 45 Type 1/2 myoma patients with complete follow-up, seven required reinterventional treatment within 24 months. The reintervention rates were 14.0% for Type 1/2 patients and 21.6% for Type 3 patients at 24 months post-treatment.

**CONCLUSIONS:** Moderate volume reductions of Type 1/2 myomas were noted following MRgFUS, and the reduction in SSS values and the relatively low reintervention rates observed are encouraging. We found MRgFUS to be an appropriate treatment method for Type 1/2 uterine myomas.

**[MR Guided]**

Okada A, Morita Y, Fukunishi H, Takeichi K, Murakami T., **Non-invasive magnetic resonance-guided focused ultrasound treatment of uterine fibroids in a large Japanese population: impact of the learning curve on patient outcome.** *Ultrasound Obstet Gynecol.* 2009 Nov;34(5):579-83.

**OBJECTIVES:** To describe the learning curve effect of magnetic resonance-guided focused ultrasound surgery (MRgFUS) on the outcomes of patients treated for uterine fibroids in four centers in Japan.

**METHODS:** The extent of fibroid ablation (often used to measure treatment success) was evaluated using the non-perfused volume (NPV) ratio in 287 Japanese patients. The patients were divided into two equal groups according to the chronological treatment time and results were compared between these groups to estimate the learning curve effect. Results were also compared with published data from clinical trials.

**RESULTS:** The NPV ratio increased chronologically, from 39.3% to 54.0% ( $P < 0.001$ ), indicating increasing effectiveness of the treatment with experience. The mean NPV ratios for the entire patient population were over double that of previous clinical trials (46.6% vs. 21.9%;  $P < 0.001$ ). No serious complications were reported.

**CONCLUSION:** The learning process and accumulation of data on MRgFUS enable the optimization of treatments in order to safely achieve large NPV ratios and sustained clinical benefit.

**[MR Guided]**

LeBlang SD, Hocter K, Steinberg FL. ***Leiomyoma Shrinkage After MR-Guided Focused Ultrasound Treatment: Report of 80 Patients***, AJR, 2010, 194:274-280.

**OBJECTIVE.** The purpose of this study was to assess the degree of leiomyoma ablation and shrinkage after MRI-guided focused ultrasound treatment performed according to U.S. Food and Drug Administration protocols for commercial trials.

**MATERIALS AND METHODS.** A total of 147 symptomatic leiomyomas in 80 women (average age, 46 years; range, 34–55 years) were managed with MRI-guided focused ultrasound. The average volume of treated fibroids was  $175 \pm 201$  (SD)  $\text{cm}^3$ . Before treatment, T2-weighted MR images in three planes were obtained to measure leiomyoma volume. Immediately after treatment, T1-weighted contrast-enhanced fat-suppressed MR images in three planes were used to measure nonperfused volume ratio. Similar images obtained 6 months after treatment were used to determine leiomyoma shrinkage. Qualitative and quantitative relations between fibroid volume, nonperfused volume ratio at treatment, and 6-month shrinkage were measured.

**RESULTS.** The average nonperfused volume ratio was  $55\% \pm 25\%$  immediately after treatment. Six months after treatment, the average volume of treated fibroids had decreased to  $112 \pm 141 \text{ cm}^3$  ( $n = 81$ ) ( $p < 0.0001$ ) with an average volume reduction of  $31\% \pm 28\%$ . A linear regression model showed highly significant correlation between posttreatment nonperfused volume ratio and shrinkage at 6 months ( $p < 0.0001$ ).

**CONCLUSION.** MRI-guided focused ultrasound therapy for leiomyoma can result in nonperfused volume ratio and shrinkage that exceed those in previous clinical trials because the treatment guidelines have been relaxed to allow a greater amount of tissue ablation. The results suggest that a larger nonperfused volume ratio can be achieved, resulting in greater shrinkage and improved relief of symptoms.

**[MR Guided]**

### **III. Adenomyosis**

Fukunishi H, Funaki K, Sawada K, Yamaguchi K, Maeda T, Kaji Y.

**Early results of magnetic resonance-guided focused ultrasound surgery of adenomyosis: analysis of 20 cases.** J Minim Invasive Gynecol. 2008 Sep-Oct;15(5):571-9.

**STUDY OBJECTIVE:** To evaluate the thermal ablative effects of magnetic resonance-(MR) guided focused ultrasound surgery (MRgFUS) on adenomyosis and to assess improvement in clinical parameters.

**DESIGN:** Twenty patients with adenomyosis were treated with MRgFUS. Extensive adenomyosis (6 cases) was treated with 2 applications. Uterine volume was evaluated by MR imaging before and immediately after MRgFUS. Ablation of adenomyosis and the architecture of nonperfused areas were evaluated immediately after MRgFUS. Improvement in patient symptoms was assessed through the symptom severity score questionnaire (Canadian Task Force classification II-3).

**SETTING:** Department of gynecology at a Japanese general hospital.

**PATIENTS:** Premenopausal women at least 18 years of age with symptomatic adenomyosis.

**INTERVENTIONS:** Thermal ablation by MRgFUS. M

**MEASUREMENTS AND MAIN RESULTS:** We classified the nonperfused lesions on contrast-enhanced MR images immediately after MRgFUS into 3 types: lesions with round margins (type R), serrated margins (type S), and honeycomb architecture (type H). Type R was the most common (16/20 patients). Most adenomyosis lesions could be sufficiently ablated close to the serosal surface or to the endometrium by MRgFUS. The mean uterine volume 6 months after therapy was decreased by 12.7%. Symptom severity score improved significantly during 6 months of follow-up. No serious complications were observed.

**CONCLUSION:** These early results indicate the safe and effective ablation of adenomyosis tissue by MRgFUS. The procedure also resulted in the improvement in clinical symptoms during the 6 months of follow-up.

**[MR Guided]**

## **IV. Bone Metastasis**

Gianfelice D, Gupta C, Kucharczyk W, Bret P, Havill D, Clemons M. *Palliative treatment of painful bone metastases with MR imaging--guided focused ultrasound*. Radiology. 2008 Oct;249(1):355-63.

**PURPOSE:** To evaluate the safety and initial efficacy of magnetic resonance (MR) imaging-guided focused ultrasound for the palliation of pain caused by bone metastases in patients in whom standard available treatments had been ineffective or not feasible.

**MATERIALS AND METHODS:** Informed consent was obtained in 11 patients (seven women, four men; average age, 58.6 years) with pain related to non-weight-bearing bone metastases who were subsequently treated with MR imaging-guided focused ultrasound in this research and ethics board-approved study. Efficacy was evaluated by changes in visual analog scale (VAS) scores, in pain medication usage, and in quality of life. Safety of the device was evaluated by recording incidence and severity of treatment-related adverse events up to 3 months after treatment at physical examination and follow-up imaging. Follow-up imaging included contrast material-enhanced MR imaging and unenhanced computed tomography (CT) 1 month after treatment and contrast-enhanced MR imaging 3 months after treatment. Imaging studies were assessed for changes in tumor imaging characteristics and any adverse events associated with MR imaging-guided focused ultrasound treatment.

**RESULTS:** Twelve lesions were treated in 11 patients. All patients reported progressive decrease in pain in treated regions and reduction in pain medication usage during the 3-month follow-up period. VAS scores averaged 6.0 before treatment and decreased to 0.5 at 3 months (decrease in pain scores, 92%;  $P < .01$ ). No adverse events were recorded at physical examination or follow-up imaging. The majority of patients with osteolytic metastases had varying degrees of necrosis of the enhancing medullary component of the metastasis at follow-up enhanced MR imaging. Five patients had increased bone density at the site of treated osteolytic metastases at follow-up unenhanced CT at 3 months after MR imaging-guided focused ultrasound.

**CONCLUSION:** MR imaging-guided focused ultrasound is a noninvasive technique that allows palliative treatment of bone metastases with little or no morbidity.

**[MR Guided]**

Liberman B, Gianfelice D, Inbar Y, Beck A, Rabin T, Shabshin N, Chander G, Hengst S, Pfeffer R, Chechick A, Hanannel A, Dogadkin O, Catane R. ***Pain Palliation in Patients with Bone Metastases Using MR guided Focused Ultrasound Surgery: A Multicenter Study***, Annals of Surgical Oncology, 2008.

**BACKGROUND:** Noninvasive thermal ablation using magnetic resonance (MR)-guided focused ultrasound (MRgFUS) has been shown to be clinically effective in uterine fibroids, and is being evaluated for ablation of breast, liver, and brain lesions. Recently MRgFUS has been evaluated for palliation of pain caused by bone metastases. We present the clinical results of a multicenter study using MRgFUS for palliation of bone metastases pain.

**METHODS:** A multicenter study to evaluate the safety and efficacy of MRgFUS palliative treatment of bone metastases was conducted in patients suffering from painful metastatic bone lesions for which other treatments were either ineffective or not feasible. Thirty-one patients with painful bone metastases underwent the MRgFUS procedure in three medical centers. Treatment safety was evaluated by assessing the device-related complications. Effectiveness of pain palliation was evaluated using the visual analog pain score (VAS), and measurable changes in the intake of opioid analgesics.

**RESULTS:** Thirty-six procedures were performed on 31 patients. Mean follow-up time was 4 months. 25 patients underwent the planned treatment and were available for 3 months post-treatment follow-up. 72% of the patients (18/25) reported significant pain improvement. Average VAS score was reduced from 5.9 prior to treatment to 1.8 at 3 months post treatment. 67% of patients with recorded medication data reported a reduction in their opioid usage. No device-related severe adverse events were recorded.

**CONCLUSION:** The results suggest that MRgFUS has the ability to provide an accurate, effective, and safe noninvasive palliative treatment for patients with bone metastases.

**[MR Guided]**

## **V. Breast**

Gianfelice D, Khiat A, Boulanger Y, Amara M, Belblidia A., ***Feasibility of magnetic resonance imaging-guided focused ultrasound surgery as an adjunct to tamoxifen therapy in high-risk surgical patients with breast carcinoma.*** J Vasc Interv Radiol. 2003 Oct;14(10):1275-82.

**PURPOSE:** To evaluate the feasibility of treating breast neoplasms with use of magnetic resonance (MR) imaging-guided focused ultrasound (US) surgery.

**MATERIALS AND METHODS:** Twenty-four female patients, each with a single biopsy-proven breast carcinoma, who were considered to be at increased surgical risk or who had refused surgery underwent MR imaging-guided focused US surgery as an adjunct to their chemotherapeutic regimen of tamoxifen. Follow-up included routine studies to rule out metastatic disease and MR studies with and without contrast material infusion in the treated breast (10 days and 1, 3, and 6 months after the treatment session). Percutaneous biopsy was performed after 6-month follow-up, and if residual tumor was present, a second MR imaging-guided focused US surgery treatment session was performed, followed by repeat biopsy 1 month later.

**RESULTS:** Twenty-three of 24 patients completed the protocol, with only one minor complication associated with the treatment sessions (second-degree skin burn resolved with local treatment). Follow-up MR studies demonstrated a varying hypointense treatment margin (range, 1-11 mm), which represents destruction of tissue beyond the visible tumor. Absence of enhancement may be an indicator of tumor destruction (18 of 19 patients with negative biopsy results) whereas persistent enhancement suggested tumor residue (three of five patients with residual tumor). Overall, 19 of 24 patients (79%) had negative biopsy results after one or two treatment sessions.

**CONCLUSION:** MR imaging-guided focused US surgery of breast tumors is a safe, repeatable, and promising method of focal tumor destruction.

**[MR Guided]**

Hokland SL, Pedersen M, Salomir R, Quesson B, Stødkilde-Jørgensen H, Moonen CT., ***MRI-guided focused ultrasound: methodology and applications***. IEEE Trans Med Imaging. 2006 Jun;25(6):723-31.

Focused ultrasound is very well suited for inducing noninvasive local hyperthermia. Since magnetic resonance imaging (MRI) may be employed to obtain real-time temperature maps noninvasively the combination of these two technologies offers great advantages specifically aimed toward oncological studies. Real-time identification of the target region and accurate control of the temperature evolution during the treatment has now become possible. Thermal ablation of pathological tissue, local drug delivery using thermosensitive micro-carriers and controlled transgene expression using thermosensitive promoters have recently been demonstrated with this unique technology. Based on these experiments combined focused ultrasound and MRI thermometry holds promise for future oncological diagnostics and treatment. In this paper, we review some of the recent methodological developments as well as experimental and first clinical studies using this approach.

**[MR Guided]**

Furusawa H, Namba K, Thomsen S, Akiyama F, Bendet A, Tanaka C, Yasuda Y, Nakahara H. ***Magnetic resonance-guided focused ultrasound surgery of breast cancer: reliability and effectiveness.*** J Am Coll Surg. 2006 Jul;203(1):54-63.

**BACKGROUND:** Magnetic resonance-guided focused ultrasound surgery (MRgFUS) is a noninvasive technique that has been shown to coagulate benign and malignant tumors. The purpose of this study was to evaluate MRgFUS safety and effectiveness for the ablation of breast carcinomas.

**STUDY DESIGN:** Thirty women with biopsy-proved breast cancer underwent MRgFUS treatment. Gadolinium-enhanced MR images were used for treatment planning and posttreatment radiologic assessment of treated tissue, and temperature-sensitive MR images provided real-time treatment monitoring. After MRgFUS, all 30 women underwent wide excision or mastectomy. The extent of thermal ablation was assessed with tumor histology.

**RESULTS:** Treatment was well tolerated, with a minimum of adverse effects, especially when performed under local anesthesia. On pathologic examination, mean (+/-SD) necrosis of the targeted breast tumors was 96.9 +/- 4% (median 100%, range 78% to 100%) of tumor volume. Fifteen (53.5%) of 28 evaluable patients had 100% necrosis of the ablated tumor; only 3 patients (10.7%) had less than 95% necrosis. In 28 (93.3%) patients, 100% of the malignancy was within the treatment field, and 98% and 95% of tumor lay within the treatment field in 2 remaining patients. Retrospective analysis in two patients with residual tumor showed treatment was not delivered to the full recommended area, reaffirming the need for precise localization and the value of contrast-enhanced images for treatment planning.

**CONCLUSIONS:** MRgFUS has great potential to become a viable noninvasive replacement for lumpectomy. Additional studies focusing on posttreatment image-based evaluation are needed.

**[MR Guided]**

Furusawa H, Namba K, Nakahara H, Tanaka C, Yasuda Y, Hirabara, E, Imahariyama M, Komaki K. ***The evolving non-surgical ablation of breast cancer: MR guided focused ultrasound (MRgFUS)***. Breast Cancer. 2007;14(1):55-8.

MRgFUS (MR guided Focused Ultrasound) being one of the non-surgical ablation techniques. We have already achieved favorable results in the past clinical study of MRgFUS to local treatment. New twenty one cases of invasive/noninvasive ductal carcinoma of the breast were treated by MRgFUS. Core needle biopsy led to the definitive diagnosis. All the patients were positioned prone in the treatment, using the therapeutic apparatus such as Signa Excite 1.5 T for MRI and ExAblate 2000 version 2.6/4.1 for FUS. Irradiation was not applied to all the 21 cases after MRgFUS. Axillary lymph node metastases were examined by dissection or sentinel lymph node biopsy. Recurrence or abnormal area of residual cancer was treated with Re-MRgFUS or ablated by usual surgery. All the 21 cases were from women patients. Median age is 54 years (range: 34-72). Median diameter of tumor is 15 mm (range: 5-50). As for the numbers of treatment, 17 patients were treated once, and 4 patients twice. Median period of observation is 14 months (range: 3-26). One case of recurrence of pure mucinous carcinoma was experienced. No evidences of recurrence were obtained through MRI for the rest of 20 cases. Skin burns were found in 2 cases. The patient had dimple on the skin immediately above tumor. In conclusion, MRgFUS is a good mean as local control of breast cancer, but the indicated case must be selected strictly. And it needs to observe longer the patients who ware treated by MRgFUS alone.

**[MR Guided]**

Schmitz AC, Gianfelice D, Daniel BL, Mali WP, van den Bosch MA, ***Image-guided focused ultrasound ablation of breast cancer: current status, challenges, and future directions***, Eur Radiol. 2008 Jul;18(7):1431-41.

Image-guided focussed ultrasound (FUS) ablation is a non-invasive procedure that has been used for treatment of benign or malignant breast tumours. Image-guidance during ablation is achieved either by using real-time ultrasound (US) or magnetic resonance imaging (MRI). The past decade phase I studies have proven MRI-guided and US-guided FUS ablation of breast cancer to be technically feasible and safe. We provide an overview of studies assessing the efficacy of FUS for breast tumour ablation as measured by percentages of complete tumour necrosis. Successful ablation ranged from 20% to 100%, depending on FUS system type, imaging technique, ablation protocol, and patient selection. Specific issues related to FUS ablation of breast cancer, such as increased treatment time for larger tumours, size of ablation margins, methods used for margin assessment and residual tumour detection after FUS ablation, and impact of FUS ablation on sentinel node procedure are presented. Finally, potential future applications of FUS for breast cancer treatment such as FUS-induced anti-tumour immune response, FUS-mediated gene transfer, and enhanced drug delivery are discussed. Currently, breast-conserving surgery remains the gold standard for breast cancer treatment.

**[Review – MR Guided and ULTRASOUND GUIDED]**

## VI. Abdominal tumors

Li JJ, Xu GL, Gu MF, Luo GY, Rong Z, Wu PH, Xia JC. **Complications of high intensity focused ultrasound in patients with recurrent and metastatic abdominal tumors.** World J Gastroenterol. 2007 May 21;13(19):2747-51.

**AIM:** To analyze the local and systemic complications of high intensity focused ultrasound (HIFU) for patients with recurrent and metastatic abdominal tumors.

**METHODS:** From Aug 2001 to Aug 2004, 17 patients with recurrent and metastatic abdominal tumors were enrolled in this study. Real-time sonography was taken, and vital signs, liver and kidney function, skin burns, local reactions, and systemic effects were observed and recorded before, during, and after HIFU. CT and MRI were also taken before and after HIFU.

**RESULTS:** All 17 patients had skin burns and pain in the treatment region; the next common complication was neurapraxia of the stomach and intestines to variable degrees. The other local and systemic complications were relatively rare. Severe complications were present in two patients; one developed a superior mesenteric artery infarction resulting in necrosis of the entire small intestines, and the other one suffered from a perforation in terminal ileum due to HIFU treatment.

**CONCLUSION:** Although HIFU is a one of noninvasive treatments for the recurrent and metastatic abdominal tumors, there are still some common and severe complications which need serious consideration.

**[ULTRASOUND GUIDED]**

## VII. Liver

Li YY, Sha WH, Zhou YJ, Nie YQ. *Short and long term efficacy of high intensity focused ultrasound therapy for advanced hepatocellular carcinoma*. J Gastroenterol Hepatol. 2007 Dec;22(12):2148-54.

**BACKGROUND:** The aim of this study was to investigate the short and long term efficacy of high intensity focused ultrasound therapy (HIFU) in patients with advanced hepatocellular carcinoma (HCC).

**METHODS:** Patients with surgically unresectable HCC received either HIFU plus supportive treatment (HIFU group, n = 151) or supportive treatment only (control group, n = 30), according to their willingness. Short term efficacy, including improvement in tumor imaging parameters, decrease in serum alpha-fetoprotein (AFP) levels, symptom relief (i.e. Karnofsky Performance Status and numerical rating scales) and response rates, and long term efficacy, including an increase in survival rates and improvement of quality of life (QOL), was monitored.

**RESULTS:** Tumor imaging parameters, serum AFP levels and symptom scores improved significantly in the HIFU group compared with the control group (all  $P < 0.05$ ). In the HIFU group, a complete and a partial response were achieved in 28.5% (n = 43) and 60.3% (n = 91) of cases, respectively, while the rates were 0% and 16.7% (n = 5), respectively, in the control group. The overall response rate (88.8%) was significantly greater in the HIFU group (16.7%) than in the control group ( $P < 0.01$ ). In addition, the 1- and 2-year survival rates were 50.0% and 30.9%, respectively, in the HIFU group, which were significantly greater than those (3.4% and 0%, respectively) in the control group (both  $P < 0.01$ ). The QOL score was 83.1 +/- 8.0 at 3 months after HIFU, which was significantly greater than the pre-HIFU score (67.7 +/- 5.9) and the score at 3 months after treatment (69.0 +/- 8.5) in the control group (both  $P < 0.05$ ). No severe complications occurred during and after HIFU.

**CONCLUSION:** HIFU is an effective and safe ablation therapy with satisfactory short and long term efficacy for patients with advanced HCC.

**[ULTRASOUND GUIDED]**

Li JJ, Gu MF, Luo GY, Liu LZ, Zhang R, Xu GL., **Complications of high intensity focused ultrasound for patients with hepatocellular carcinoma.** Technol Cancer Res Treat. 2009 Jun;8(3):217-24.

High intensity focused ultrasound (HIFU) is a noninvasive treatment modality that induces complete coagulative necrosis of a deep tumor through the intact skin. This study was conducted to analyze and evaluate the complications of HIFU for the treatments of hepatocellular carcinoma. A total of 59 patients with hepatocellular carcinoma, with a total of 72 lesions were enrolled in this study. Tumor size ranged from 2.5 to 14.0 cm in diameter, with a mean diameter of 7.6 cm. All patients had accepted HIFU treatment, and the median number of HIFU sessions was 1.32 per patient.

**RESULTS:** The common complications from HIFU therapy were skin burns of various grades (eight cases of grade 1 skin burns, 48 of grade 2, three cases of 3), and pain in the treatment regions (15 cases of mild pain, 37 cases of moderate pain, 7 cases of severe pain). Other systemic complications were relatively rare and included fever (5 cases), hypertension (8 cases), supraventricular tachycardia (3 cases), mild impairment of hepatic function (48 cases), and mild impairment of renal function (2 cases). Local damage consisted of acute cholecystitis (2 cases), hematuria (6 cases), cholangiectasis (5 cases), light pericardial effusion (2 cases), impairment of peripheral nerves (10 cases), pleural effusion in the right thorax (3 cases), and impairment of vertebral column (1 case). No gastric or intestinal tract perforation, big vessel rupture, or hepatic rupture occurred.

**CONCLUSIONS:** HIFU is a minimally invasive treatment for patients with hepatocellular carcinoma; however, there are some systemic and local complications that should be taken into consideration in evaluating HIFU for therapeutic use.

**[ULTRASOUND GUIDED]**

## VIII. Prostate Cancer

Obyn C, Mambourg F. **Assessment of high intensity focused ultrasound for the treatment of prostate cancer**. Acta Chir Belg. 2009 Oct;109(5):581-6.

The optimal treatment for localized prostate tumours remains unknown. The standard curative options (radical prostatectomy and radiotherapy) are not free of significant complications and risks. High-intensity focused ultrasound (HIFU) appears to be an alternative. It is currently used as primary treatment for patients with localized prostate cancer T(1-2) N(0-x) M0, mostly low and intermediate risk, not suitable for surgery and as salvage treatment for locally proven recurrence of prostate cancer after curative therapy. In Belgium, it is estimated that about 730 patients (0.8% of all new prostate cancer patients) were treated with this new technology at 4 hospitals in the years 2000 to 2008. Given the increasing use of HIFU, this study was conducted to assess the current evidence supporting the effectiveness and safety of HIFU and to examine its role in the management of prostate cancer. A standard literature review showed that there is currently not sufficient evidence to support routine use of this new treatment modality. In order to obtain FDA approval, two multicentric non-randomized controlled trials comparing HIFU with cryotherapy and brachytherapy have been started in the U.S. and are now recruiting patients. Until more evidence becomes available, KCE recommends to limit the use of HIFU treatment to study setting. Future research is recommended in the form of comparative studies, preferably randomized controlled trials.

**[ULTRASOUND GUIDED]**

Ripert T, Azémar MD, Ménard J, Bayoud Y, Messaoudi R, Duval F, Staerman F. ***Transrectal high-intensity focused ultrasound (HIFU) treatment of localized prostate cancer: review of technical incidents and morbidity after 5 years of use.*** Prostate Cancer Prostatic Dis. 2010 Jan

The objective of this study was to report on technical incidents and early and late complications occurring in high-intensity focused ultrasound (HIFU) treatment of patients with localized prostate cancer. We performed a retrospective review of patients who were treated by Ablatherm at our centre. We recorded all technical incidents, treatment discontinuations and early (<1 month) and late complications. A total of 74 HIFU procedures were performed in 65 patients (55 first-line HIFU treatments and 10 cases of salvage therapy after radiotherapy) over a 5-year period. Median follow-up was 41 months (10-64 months). All the procedures were well tolerated and no intra- or peri-operative deaths occurred. Six technical incidents in the overall population (8.1%) led to discontinuation of the procedure. The early complication rate in patients undergoing first-line HIFU was 36.4%: urinary retention (20%), dysuria (5.4%), urinary infection (3.6%), haematuria (3.6%) and urethral stenosis (3.6%). The late complication rate was 12.7%: urethral stenosis (9%) and dysuria (3.6%). There were no cases of rectourethral fistula. The long-term urinary incontinence rate was 20% and the de novo erectile dysfunction rate was 77.1%. Nine complications (16.4%) required surgical management. The overall complication rate was 49%. Ablatherm is a reliable technique with a relatively high complication rate. However, most complications were minor and required surgical management in a few cases only. Our results confirm that all patients who are offered HIFU treatment should be properly informed of the risks, in particular with regard to continence and sexual function.

**[ULTRASOUND GUIDED]**

## IX. Brain

Ram Z, Cohen ZR, Harnof S, Tal S, Faibel M, Nass D, Maier SE, Hadani M, Mardor Y., ***Magnetic resonance imaging-guided, high-intensity focused ultrasound for brain tumor therapy.*** Neurosurgery. 2006 Nov;59(5):949-55;

**OBJECTIVE:** Magnetic resonance imaging-guided high-intensity focused ultrasound (MRIGFUS) is a novel technique that may have the potential for precise image-guided thermocoagulation of intracranial lesions. The system delivers small volumetric sonications from an ultrasound phased array transmitter that focuses energy selectively to destroy the target with verification by magnetic resonance imaging-generated thermal maps. A Phase I clinical study was initiated to treat patients with recurrent glioma with MRIGFUS.

**METHODS:** To date, three patients with histologically verified recurrent glioblastoma multiforme have been treated with MRIGFUS. All patients underwent craniectomy 7 to 10 days before therapy to create a bony window for the ultrasound treatment. Sonications were applied to induce thermocoagulation of the enhancing tumor mass. Long-term radiological follow-up and post-treatment tissue specimens were available for all patients.

**RESULTS:** MRIGFUS treatment resulted in immediate changes in contrast-enhanced T1-, T2-, and diffusion-weighted magnetic resonance imaging scans in the treated regions with subsequent histological evidence of thermocoagulation. In one patient, heating of brain tissue in the sonication path resulted in a secondary focus outside the target causing neurological deficit. New software modifications were developed to address this problem.

**CONCLUSION:** In this first clinical report, MRIGFUS was demonstrated to be a potentially effective means of destroying tumor tissue by thermocoagulation, although with an associated morbidity and the inherent invasive nature of the procedure requiring creation of a bone window. A modified technology to allow MRIGFUS treatment through a closed cranium is being developed.

**[MR Guided]**

Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B., ***High-intensity focused ultrasound for noninvasive functional neurosurgery.*** Ann Neurol. 2009 Dec;66(6):858-61.

Transcranial magnetic resonance (MR)-guided high-intensity focused ultrasound (tcMRgHIFU) implies a novel, noninvasive treatment strategy for various brain diseases. Nine patients with chronic neuropathic pain were treated with selective medial thalamotomies. Precisely located thermal ablations of 4mm in diameter were produced at peak temperatures of 51 degrees C to 60 degrees C under continuous visual MR guidance and MR thermometry. The resulting lesions are clearly visible on follow-up MR imaging. All treatments were well tolerated, without side effects or neurological deficits. This is the first report on successful clinical application of tcMRgHIFU in functional brain disorders, portraying it as safe and reliable for noninvasive neurosurgical interventions.

**[MR Guided]**

Jagannathan J, Sanghvi NT, Crum LA, Yen CP, Medel R, Dumont AS, Sheehan JP, Steiner L, Jolesz F, Kassell NF., ***High-intensity focused ultrasound surgery of the brain: part 1--A historical perspective with modern applications.*** Neurosurgery. 2009 Feb;64(2):201-10;

The field of magnetic resonance imaging-guided high-intensity focused ultrasound surgery (MRgFUS) is a rapidly evolving one, with many potential applications in neurosurgery. The first of 3 articles on MRgFUS, this article focuses on the historical development of the technology and its potential applications in modern neurosurgery. The evolution of MRgFUS has occurred in parallel with modern neurological surgery, and the 2 seemingly distinct disciplines share many of the same pioneering figures. Early studies on focused ultrasound treatment in the 1940s and 1950s demonstrated the ability to perform precise lesioning in the human brain, with a favorable risk-benefit profile. However, the need for a craniotomy, as well as the lack of sophisticated imaging technology, resulted in limited growth of high-intensity focused ultrasound for neurosurgery. More recently, technological advances have permitted the combination of high-intensity focused ultrasound along with magnetic resonance imaging guidance to provide an opportunity to effectively treat a variety of central nervous system disorders. Although challenges remain, high-intensity focused ultrasound-mediated neurosurgery may offer the ability to target and treat central nervous system conditions that were previously extremely difficult to address. The remaining 2 articles in this series will focus on the physical principles of modern MRgFUS as well as current and future avenues for investigation.

**[Review]**

McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. ***Transcranial magnetic resonance imaging- guided focused ultrasound surgery of brain tumors: initial findings in 3 patients.*** Neurosurgery. 2010 Feb;66(2):323-32;

**OBJECTIVE:** This work evaluated the clinical feasibility of transcranial magnetic resonance imaging-guided focused ultrasound surgery.

**METHODS:** Transcranial magnetic resonance imaging-guided focused ultrasound surgery offers a potential noninvasive alternative to surgical resection. The method combines a hemispherical phased-array transducer and patient-specific treatment planning based on acoustic models with feedback control based on magnetic resonance temperature imaging to overcome the effects of the cranium and allow for controlled and precise thermal ablation in the brain. In initial trials in 3 glioblastoma patients, multiple focused ultrasound exposures were applied up to the maximum acoustic power available. Offline analysis of the magnetic resonance temperature images evaluated the temperature changes at the focus and brain surface.

**RESULTS:** We found that it was possible to focus an ultrasound beam transcranially into the brain and to visualize the heating with magnetic resonance temperature imaging. Although we were limited by the device power available at the time and thus seemed to not achieve thermal coagulation, extrapolation of the temperature measurements at the focus and on the brain surface suggests that thermal ablation will be possible with this device without overheating the brain surface, with some possible limitation on the treatment envelope.

**CONCLUSION:** Although significant hurdles remain, these findings are a major step forward in producing a completely noninvasive alternative to surgical resection for brain disorders.

**[MR Guided]**