JC – HAIFU
High Intensity Focused Ultrasound

SCIENTIFIC REPORTS

ABSTRACTS 2014
1) Multi-parametric monitoring and assessment of high-intensity focused ultrasound (HIFU) boiling by harmonic motion imaging for focused ultrasound (HMIFU): an ex vivo feasibility study.

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Author information

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Abstract

Harmonic motion imaging for focused ultrasound (HMIFU) is a recently developed high-intensity focused ultrasound (HIFU) treatment monitoring method with feasibilities demonstrated in vitro and in vivo. Here, a multi-parametric study is performed to investigate both elastic and acoustics-independent viscoelastic tissue changes using the Harmonic Motion Imaging (HMI) displacement, axial compressive strain and change in relative phase shift during high energy HIFU treatment with tissue boiling. Forty three (n = 43) thermal lesions were formed in ex vivo canine liver specimens (n = 28). Two-dimensional (2D) transverse HMI displacement maps were also obtained before and after lesion formation. The same method was repeated in 10 s, 20 s and 30 s HIFU durations at three different acoustic powers of 8, 10, and 11 W, which were selected and verified as treatment parameters capable of inducing boiling using both thermocouple and passive cavitation detection (PCD) measurements. Although a steady decrease in the displacement, compressive strain, and relative change in the focal phase shift (Δϕ) were obtained in numerous cases, indicating an overall increase in relative stiffness, the study outcomes also showed that during boiling, a reverse lesion-to-background displacement contrast was detected, indicating potential change in tissue absorption, geometrical change and/or, mechanical gelatification or pulverization. Following treatment, corresponding 2D HMI displacement images of the thermal lesions
also mapped consistent discrepancy in the lesion-to-background displacement contrast. Despite the expectedly chaotic changes in acoustic properties with boiling, the relative change in phase shift showed a consistent decrease, indicating its robustness to monitor biomechanical properties independent of the acoustic property changes throughout the HIFU treatment. In addition, the 2D HMI displacement images confirmed and indicated the increase in the thermal lesion size with treatment duration, which was validated against pathology. In conclusion, multi-parametric HMIFU was shown capable of monitoring and mapping tissue viscoelastic response changes during and after HIFU boiling, some of which were independent of the acoustic parameter changes.


2) Enhancing Ablation Effects of a Microbubble-Enhancing Contrast Agent ("SonoVue") in the Treatment of Uterine Fibroids With High-Intensity Focused Ultrasound: A Randomized Controlled Trial.


Author information

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Abstract

PURPOSE:

To evaluate the role of the ultrasound contrast agent SonoVue in enhancing the ablation effects of ultrasound-guided high-intensity focused ultrasound (HIFU) on uterine fibroids.
METHODS:

Eighty patients with solitary uterine fibroids at a single center were randomly assigned to a control or SonoVue group. Of these, 40 were treated using HIFU alone; 40 who were pretreated with SonoVue received a bolus before the HIFU procedure. All patients underwent magnetic resonance imaging (MRI) scan before and after HIFU treatment.

RESULTS:

The post-HIFU MRI showed the nonperfused volume (NPV) in all of the treated uterine fibroids; the mean fractional ablation (NPV ratio) was $90.4 \pm 8.3\%$ (range 66.4-100\%) in the SonoVue group and $82.8 \pm 13.3\%$ (range 53.4-100\%) in the control group. The frequency of massive gray-scale changes that occurred during HIFU was greater in the group that received SonoVue than the group that did not. The average sonication time to reach massive gray-scale changes was significantly shorter in the group receiving SonoVue than the group without SonoVue. The acoustic energy for treating 1 mm$^3$ of uterine fibroid was less in the SonoVue group than the control group. No any major complication occurred in this study.

CONCLUSION:

Based on the results of this randomized controlled trial, SonoVue could be safely used to enhance the effects of HIFU treatment for uterine fibroids.


3) High-Intensity Focused Ultrasound Ablation of Myocardium In Vivo and Instantaneous Biological Response.

Zheng M$^1$, Shentu W, Chen D, Sahn DJ, Zhou X.
Abstract

OBJECTIVE:

This study aimed to evaluate the instantaneous biological response of canine myocardium in vivo to high-intensity focused ultrasound (HIFU) ablation, and thereby determine the feasibility of this method.

METHODS:

Left ventricle myocardium HIFU ablation was performed on six dogs at four levels of HIFU energy (acoustic intensity was 3000 W/cm²; ablation durations were 1.2, 2.4, 3.6, and 4.8 sec, respectively). Gross lesion volumes were confirmed and assessed by tetrazolium chloride (TTC) staining, hematoxylin-eosin (HE) staining, and electron microscopy. Global cardiac function and focal wall motion were evaluated by echocardiography. Blood enzymes and cardiac troponin T (CTnT) were tested after ablation. HIFU ablation was repeated on another set of six fresh canine hearts in vitro at the same four energy levels. Focal maximum temperatures were detected both in vivo and in vitro.

RESULTS:

Different sizes of ablation via HIFU can be created in beating hearts using controlled energy emission. Focal maximum temperatures varied from $62 \pm 4.8^\circ$C to $81 \pm 12.9^\circ$C. The lesion sizes were significantly smaller in vivo than in vitro, as verified by TTC and HE staining. Focal wall motion immediately decreased after ablation ($P < 0.05$), although the ejection fraction (EF) and E/A ratio were unchanged ($P > 0.05$). Enzymes and CTnT immediately increased.

CONCLUSION:
HIFU can be used for the controllable ablation of myocardial tissue, with instantly increased serum markers, decreased regional wall motion, and unaffected left ventricular global function.

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4) **High-Intensity Focused Ultrasound Treatment of Late-Stage Pancreatic Body Carcinoma: Optimal Tumor Depth for Safe Ablation.**

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**Abstract**

Objective criteria are currently not available for assessing the extent of ablation by high-intensity focused ultrasound (HIFU). A retrospective review was conducted in Chinese patients with late-stage pancreatic body carcinoma treated with 1 h/d intermittent HIFU at a single center. Clinical and procedure-related characteristics were examined in relation to tumor posterior depth. Clinically, tumor ablation was negatively correlated with posterior tumor depth, with a
1-cm increase in depth decreasing ablation by 30.7%. At a computed tomography (CT)-determined 7-cm posterior tumor depth (considered the critical value for the procedure), ablation sensitivity and specificity were 77.8% and 72.7%, respectively. Tumor ablation >30% in patients with a CT-determined posterior tumor depth ≤7 cm was 9.333 times better than that in patients with a CT-determined posterior tumor depth >7 cm. Adverse effects did not affect the efficacy of HIFU. Tumors with posterior depths <7 cm may effectively be treated with HIFU-induced ablation with minimal adverse events.

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5) Survival analysis of high-intensity focused ultrasound therapy vs. transarterial chemoembolization for unresectable hepatocellular carcinomas.

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Author information

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Abstract

BACKGROUND & AIMS:

High-intensity focused ultrasound (HIFU) ablation is a non-invasive treatment for unresectable hepatocellular carcinomas (HCCs), but long-term survival analysis is lacking. This study was to analyse its outcome compared to that of transarterial chemoembolization (TACE).

METHODS:
From October 2003 to September 2010, 113 patients received HIFU ablation as a treatment of HCCs at our hospital. Twenty-six patients had HCCs sized 3-8 cm. Fifty-two patients with matched tumour characteristics having TACE as primary treatment were selected for comparison. Short-term outcome and long-term survival were analysed.

RESULTS:

In the HIFU group (n = 26), 46 tumours were ablated. The median age of the patients was 69 (49-84) years. The median tumour size was 4.2 (3-8) cm. In the TACE group (n = 52), the median age of the patients was 67 (44-84) years. The median tumour size was 4.8 (3-8) cm. There was no hospital mortality in any of the groups. In the HIFU group, the rates of complete tumour response, partial tumour response, stable disease and progressive disease were 50%, 7.7%, 25.6% and 7.7% respectively, according to the modified Response Evaluation Criteria in Solid Tumours. The TACE group had the corresponding rates at 0%, 21.2%, 63.5% and 15.4% respectively (P < 0.0001). The 1-year, 3-year and 5-year survival rates were 84.6%, 49.2% and 32.3% respectively, in the HIFU group and 69.2%, 29.8% and 2.3% respectively, in the TACE group (P = 0.001).

CONCLUSION:

HIFU ablation is a safe and effective method for unresectable HCCs. A survival benefit is observed over sole TACE.

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6) An ex Vivo Human Lung Model for Ultrasound-Guided High-Intensity Focused Ultrasound Therapy Using Lung Flooding.

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3Department of Thoracic and Vascular Surgery, SRH Wald-Klinikum Gera, Teaching Hospital of Friedrich-Schiller-University of Jena, Gera, Germany.

Abstract

The usability of an ex vivo human lung model for ablation of lung cancer tissue with high-intensity focused ultrasound (HIFU) is described. Lung lobes were flooded with saline, with no gas remaining after complete atelectasis. The tumor was delineated sonomorphologically. Speed of sound, tissue density and ultrasound attenuation were measured for flooded lung and different pulmonary cancer tissues. The acoustic impedance of lung cancer tissue (1.6-1.9 mega-Rayleighs) was higher than that of water, as was its attenuation coefficient (0.31-0.44 dB/cm/MHz) compared with that of the flooded lung (0.12 dB/cm/MHz). After application of HIFU, the temperature in centrally located lung cancer surrounded by the flooded lung increased as high as 80°C, which is sufficient for treatment. On the basis of these preliminary results, ultrasound-guided HIFU ablation of lung cancer, by lung flooding with saline, appears feasible and should be explored in future clinical studies.

Combination of bubble liposomes and high-intensity focused ultrasound (HIFU) enhanced antitumor effect by tumor ablation.


Author information

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Abstract

Ultrasound (US) is used in the clinical setting not only for diagnosis but also for therapy. As a therapeutic US technique, high-intensity focused ultrasound (HIFU) can be applied to treat cancer in a clinical setting. Microbubbles increased temperature and improved the low therapeutic efficiency under HIFU; however, microbubbles have room for improvement in size, stability, and targeting ability. To solve these issues, we reported that "Bubble liposomes" (BLs) containing the US imaging gas (perfluoropropane gas) liposomes were suitable for ultrasound imaging and gene delivery. In this study, we examined whether BLs and HIFU could enhance the ablation area of the tumor and the antitumor effect. First, we histologically analyzed the tumor after BLs and HIFU. The ablation area of the treatment of BLs and HIFU was broader that of HIFU alone. Next, we monitored the temperature of the tumor, and examined the antitumor effect. The temperature increase with BLs and HIFU treatment was faster and higher than that with HIFU alone. Moreover, treatment with BLs and HIFU enhanced the antitumor effect, which was better than with HIFU alone. Thus, the combination of BLs and HIFU could be efficacious for cancer therapy.

Effective ablation therapy of adenomyosis with ultrasound-guided high-intensity focused ultrasound.

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Abstract

OBJECTIVE:

To evaluate the effects of ultrasound-guided high-intensity focused ultrasound (HIFU) on adenomyosis.

METHODS:

In a retrospective analysis, data were reviewed from 202 patients with adenomyosis who underwent ultrasound-guided HIFU between November 2010 and June 2012 at Suining Central Hospital, Sichuan, China. Among these patients, 120 and 82 were classified as having focal adenomyosis and diffuse adenomyosis, respectively. All patients underwent pre-treatment and post-treatment magnetic resonance imaging by a standardized protocol to evaluate the treatment. All adverse effects were recorded.

RESULTS:
All patients completed the ultrasound-guided HIFU treatment in 1 session. A non-perfused volume ratio of 71.6%±19.1% was achieved. Compared with baseline data, the average menorrhagia severity score and the average dysmenorrhea severity pain score decreased significantly after ultrasound-guided HIFU (both P<0.001). The proportion of women with complete relief of dysmenorrhea at the 3-month follow-up was significantly higher among women with focal adenomyosis than among those with diffuse adenomyosis (P=0.02). No other significant differences were observed between the 2 patient groups.

CONCLUSION:

Ultrasound-guided HIFU was found to be an effective technique for treating both focal and diffuse adenomyotic lesions to alleviate the symptoms of menorrhagia or dysmenorrhea.

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9) **High-intensity focused ultrasound for potential treatment of polycystic ovary syndrome: toward a noninvasive surgery.**

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- ²College of Science and Engineering, University of Minnesota, Minneapolis, Minnesota.
OBJECTIVE: To investigate the feasibility of using high-intensity focused ultrasound (HIFU), under dual-mode ultrasound arrays (DMUAs) guidance, to induce localized thermal damage inside ovaries without damage to the ovarian surface.

DESIGN: Laboratory feasibility study.

SETTING: University-based laboratory.

ANIMAL(S): Ex vivo canine and bovine ovaries.

INTERVENTION(S): DMUA-guided HIFU.

MAIN OUTCOME MEASURE(S): Detection of ovarian damage by ultrasound imaging, gross pathology, and histology.

RESULT(S): It is feasible to induce localized thermal damage inside ovaries without damage to the ovarian surface. DMUA provided sensitive imaging feedback regarding the anatomy of the treated ovaries and
the ablation process. Different ablation protocols were tested, and thermal damage within the treated ovaries was histologically characterized.

**CONCLUSION(S):**

The absence of damage to the ovarian surface may eliminate many of the complications linked to current laparoscopic ovarian drilling (LOD) techniques. HIFU may be used as a less traumatic tool to perform LOD.

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**Ultrason Sonochem.** 2014 Apr 6. pii: S1350-4177(14)00122-9. doi: 10.1016/j.ultsonch.2014.03.032. [Epub ahead of print]

**10) Spatial and temporal observation of phase-shift nano-emulsions assisted cavitation and ablation during focused ultrasound exposure.**

Qiao Y¹, Zong Y¹, Yin H¹, Chang N¹, Li Z¹, Wan M².

**Author information**

**Abstract**

Background: Phase-shift nano-emulsions (PSNEs) with a small initial diameter in nanoscale have the potential to leak out of the blood vessels and to accumulate at the target point of tissue. At desired location, PSNEs can undergo acoustic droplet vaporization (ADV) process, change into gas bubbles and enhance focused ultrasound efficiency. The threshold of droplet vaporization and influence of acoustic parameters have always been research hotspots in order to spatially control the potential of bioeffects and optimize experimental conditions. However, when the pressure is much higher than PSNEs' vaporization threshold, there were little reports on their cavitation and thermal effects. Object: In this study, PSNEs induced cavitation and ablation effects during pulsed high-intensity focused ultrasound (HIFU) exposure were investigated, including the spatial and temporal information and the influence of acoustic parameters. Methods: Two kinds of tissue-
mimicking phantoms with uniform PSNEs were prepared because of their optical transparency. The Sonoluminescence (SL) method was employed to visualize the cavitation activities. And the ablation process was observed as the heat deposition could produce white lesion. Results: Precisely controlled HIFU cavitation and ablation can be realized at a relatively low input power. But when the input power was high, PSNEs can accelerate cavitation and ablation in pre-focal region. The cavitation happened layer by layer advancing the transducer. While the lesion appeared to be separated into two parts, one in pre-focal region stemmed from one point and grew quickly, the other in focal region grew much more slowly. The influence of duty cycle has also been examined. Longer pulse off time would cause heat transfer to the surrounding media, and generate smaller lesion. On the other hand, this would give outer layer bubbles enough time to dissolve, and inner bubbles can undergo violent collapse and emit bright light.

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**Expert Rev Anticancer Ther.** 2014 Apr 19. [Epub ahead of print]

11) **Locally ablative therapies for primary and metastatic liver cancer.**

Li D¹, Kang J, Madoff DC.

**Author information**

**Abstract**

Locally ablative therapies have an increasing role in the effective multidisciplinary approach towards the treatment of both primary and metastatic liver tumors. In patients who are not considered surgical candidates and have low volume disease, these therapies have now become established into consensus practice guidelines. A large range of therapeutic options exist including percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, percutaneous laser ablation (PLA), irreversible electroporation (IRE), stereotactic body radiation therapy (SBRT) and high intensity focused ultrasound (HIFU); each having benefits and drawbacks. The greatest body of evidence supporting clinical utility in the liver currently exists for RFA, with PEI having fallen out of favor. MWA, IRE, SBRT and HIFU are relatively nascent technologies, and
outcomes data supporting their use is promising. Future directions of ablative therapies include tandem approaches to improve efficacy in the treatment of liver tumors.

World J Urol. 2014 Apr 4. [Epub ahead of print]

12) The contemporary role of ablative treatment approaches in the management of renal cell carcinoma (RCC): focus on radiofrequency ablation (RFA), high-intensity focused ultrasound (HIFU), and cryoablation.

Klatte T, Kroeger N, Zimmermann U, Burchardt M, Belldegrun AS, Pantuck AJ.

Author information

Abstract

INTRODUCTION:
Currently, most of renal tumors are small, low grade, with a slow growth rate, a low metastatic potential, and with up to 30% of these tumors being benign on the final pathology. Moreover, they are often diagnosed in elderly patients with preexisting medical comorbidities in whom the underlying medical conditions may pose a greater risk of death than the small renal mass. Concerns regarding overdiagnosis and overtreatment of patients with indolent small renal tumors have led to an increasing interest in minimally invasive, ablative as an alternative to extirpative interventions for selected patients.

OBJECTIVE:
To provide an overview about the state of the art in radiofrequency ablation (RFA), high-intensity focused ultrasound, and cryoablation in the clinical management of renal cell carcinoma.

METHODS:
A PubMed wide the literature search of was conducted.

RESULTS:
International consensus panels recommend ablative techniques in patients who are unfit for surgery, who are not considered candidates for or elect against elective surveillance, and who have small renal masses. The most often used techniques are cryoablation and RFA. These ablative techniques offer potentially curative outcomes while conferring several advantages over extirpative surgery, including improved patient procedural tolerance, faster recovery, preservation of renal function, and reduction in the risk of intraoperative and postsurgical complications. While it is likely that outcomes associated with ablative modalities will improve with further advances in
technology, their application will expand to more elective indications as longer-term efficacy data become available.

**CONCLUSION:**
Ablative techniques pose a valid treatment option in selected patients.


**13) Ultrasound induced cancer immunotherapy.**

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**Author information**

**Abstract**
Recently, the use of ultrasound (US) has been shown to have potential in cancer immunotherapy. High intensity focused US destruction of tumors may lead to immunity forming in situ in the body by immune cells being exposed to the tumor debris and immune stimulatory substances that are present in the tumor remains. Another way of achieving anti-cancer immune responses is by using US in combination with microbubbles and nanobubbles to deliver genes and antigens into cells. US leads to bubble destruction and the forces released to direct delivery of the substances into the cytoplasm of the cells thus circumventing the natural barriers. In this way tumor antigens and antigen-encoding genes can be delivered to immune cells and immune response stimulating genes can be delivered to cancer cells thus enhancing immune responses. Combination of bubbles with cell-targeting ligands and US provides an even more sophisticated delivery system whereby the therapy is not only site specific but also cell specific. In this review we describe how US has been used to achieve immunity and discuss the potential and possible obstacles in future development.


**14) Methotrexate-loaded PLGA nanobubbles for ultrasound imaging and Synergistic Targeted therapy of residual tumor during HIFU ablation.**


**Author information**

**Abstract**
High intensity focused ultrasound (HIFU) has attracted the great attention in tumor ablation due to its non-invasive, efficient and economic features. However, HIFU ablation has its intrinsic limitations for removing the residual tumor cells, thus the tumor recurrence and metastasis cannot be avoided in this case. Herein, we developed a multifunctional targeted poly(lactic-co-glycolic acid) (PLGA) nanobubbles (NBs), which not only function as an efficient ultrasound contrast agent for tumor imaging, but also a targeted anticancer drug carrier and excellent synergistic agent for enhancing the therapeutic efficiency of HIFU ablation. Methotrexate (MTX)-loaded NBs were synthesized and filled with perfluorocarbon gas subsequently using a facile but general double emulsion evaporation method. The active tumor-targeting monoclonal anti-HLA-G antibodies (mAbHLA-G) were further conjugated onto the surface of nanobubbles. The mAbHLA-G/MTX/PLGA NBs could enhance the ultrasound imaging both in vitro and in vivo, and the targeting efficiency to HLA-G overexpressing JEG-3 cells has been demonstrated. The elaborately designed mAbHLA-G/MTX/PLGA NBs can specifically target to the tumor cells both in vitro and in vivo, and their blood circulation time in vivo was much longer than non-targeted MTX/PLGA NBs. Further therapeutic evaluations showed that the targeted NBs as a synergistic agent can significantly improve the efficiency of HIFU ablation by changing the acoustic environment, and the focused ultrasound can promote the on-demand MTX release both in vitro and in vivo. The in vivo histopathology test and immunohistochemical analysis showed that the mAbHLA-G/MTX/PLGA NBs plus HIFU group presented most serious coagulative necrosis, the lowest proliferation index and the highest apoptotic index. Therefore, the successful introduction of targeted mAbHLA-G/MTX/PLGA NBs provides an excellent platform for the highly efficient, imaging-guided and non-invasive HIFU synergistic therapy of cancer with the supplementary functions of killing residual tumor cells and preventing tumor recurrence/metastasis.

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15) Image-Guided Ablation in Breast Cancer Treatment.
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Author information

Abstract

In the past 2 decades, new and improved imaging technologies and the use of breast cancer screening have led to the detection of smaller and earlier-stage breast cancers. Furthermore, there has been a trend toward less aggressive treatment of small breast cancers, which has led to the development of less invasive alternatives than surgery with promising effectiveness, and less morbidity. Many patients are not satisfied with the cosmetic outcome after breast-conservation therapy. Better cosmesis can be achieved with less invasive techniques. Moreover, less aggressive treatment options would be very useful in patients older than 70 years with comorbidities that make surgery a difficult and sometimes life-threatening treatment. Minimally invasive ablation techniques have been studied in early-stage small tumors with the goal of attaining efficacy similar to that of breast-conservation therapy. These techniques would have less scarring and pain, lower costs, better preservation of breast tissue, superior cosmesis, and faster recovery time. Breast lesions can be destroyed by thermal methods, that is, by heating or freezing the tissue. There are 5 types of thermal ablations that have been or currently are in research clinical trials: cryoablation, radiofrequency, laser, microwave, and high-intensity focused ultrasound ablation. The first 4 methods destroy cancers using percutaneous image-guided probe placement. High-intensity focused ultrasound is noninvasive, performed without any skin opening.