

REVIEWS

Kennedy, J. E. (2005). "High-intensity focused ultrasound in the treatment of solid tumours." Nat Rev Cancer 5(4):321-7.

Traditionally, surgery has been the only cure for many solid tumours. Technological advances have catalysed a shift from open surgery towards less invasive techniques. Laparoscopic surgery and minimally invasive techniques continue to evolve, but for decades high-intensity focused ultrasound has promised to deliver the ultimate objective - truly non-invasive tumour ablation. Only now, however, with recent improvements in imaging, has this objective finally emerged as a real clinical possibility.

Kennedy, J. E., G. R. Ter Haar, et al. (2003). "High intensity focused ultrasound: surgery of the future?" Br J Radiol 76(909): 590-9.

For 50 years, high intensity focused ultrasound (HIFU) has been a subject of interest for medical research. HIFU causes selective tissue necrosis in a very well defined volume, at a variable distance from the transducer, through heating or cavitation. Over the past decade, the use of HIFU has been investigated in many clinical settings. This literature review aims to summarize recent advances made in the field. A Medline-based literature search (1965-2002) was conducted using the keywords "HIFU" and "high intensity focused ultrasound". Additional literature was obtained from original papers and published meeting abstracts. The most abundant clinical trial data comes from studies investigating its use in the treatment of prostatic disease, although early research looked at applications in neurosurgery. More recently horizons have been broadened, and the potential of HIFU as a non-invasive surgical tool has been demonstrated in many settings including the treatment of tumours of the liver, kidney, breast, bone, uterus and pancreas, as well as conduction defects in the heart, for surgical haemostasis, and the relief of chronic pain of malignant origin. Further clinical evaluation will follow, but recent technological development suggests that HIFU is likely to play a significant role in future surgical practice.

CLINICAL

GENERAL

Wu,F., Chen, W.Z., et al. (2001). "Pathological changes in human malignant carcinoma treated with high-intensity focused ultrasound." *Ultrasound Med Biol*; 27(8):1099–1106.

Abstract—The purpose of this study was to investigate the pathologic changes of extracorporeal ablation of human malignant tumors with high-intensity focused ultrasound (HIFU). HIFU treatment was performed in the 164 patients with liver cancer, breast cancer, malignant bone tumor, soft tissue sarcoma and other malignant tumors at focal peak intensities from 5000 W cm² to 20,000 W cm², with operating frequencies of 0.8 to 3.2 MHz. To explore the pathologic impact of extracorporeal HIFU, 30 patients with malignant carcinoma underwent surgical removal after HIFU treatment. Pathologic findings showed that the treated tissues demonstrated homogenous coagulative necrosis with an irreversible tumor cell death and severe damage to tumor blood vessels at the level of microvasculature within the HIFU-targeted region. Thermolesions to intervening tissue were never observed. The treated region had a sharp border comprising only several cell layers between the treated and untreated areas. The repair of lesions had the processes of necrotic tissue absorption and granulation tissue replacement. It is concluded that extracorporeal treatment of human solid malignancies with HIFU could be safe, effective and feasible. As a noninvasive therapy, HIFU would be used clinically to treat patients with solid malignancies.

Wu,F., Chen, W.Z., et al. (2002). "Tumor vessel destruction resulting from high-intensity focused ultrasound in patients with solid malignancies." *Ultrasound Med Biol*; 28(4):535–542.

Abstract—The purpose of this study was to explore the sequential imaging and histologic alterations of tumor blood vessels in the patient with solid malignancies after extracorporeal treatment of high-intensity focused ultrasound (HIFU). A total of 164 patients underwent extracorporeal HIFU ablation of malignant solid tumors. After HIFU treatment, enhanced magnetic resonance imaging (MRI), color Doppler ultrasound (US) imaging, dynamic radionuclide scanning, digital subtraction angiography, and histologic study were performed to monitor the response of tumor vessels to HIFU ablation. Compared with tumor images in the patients before HIFU, clinical images showed an abrupt interruption, followed by the cessation of blood flow within the tumor

vessels after HIFU treatment. The histologic examination indicated that not only the treated tumor cells showed coagulative necrosis, but also small tumor vessels were severely damaged by the HIFU treatment. The results strongly imply that the damaged tumor vessels might play a critical role in secondary tumor cell death, and then indirectly strengthen the destructive force of focused US beams on tumor tissue. It is concluded that tumor vessel damage can be induced by HIFU, which may be a promising strategy in the treatment of patients with solid malignancies.

Wu, F., Z. B. Wang, et al. (2004). "Extracorporeal focused ultrasound surgery for treatment of human solid carcinomas: early Chinese clinical experience." *Ultrasound Med Biol* 30(2): 245-60.

The objective of this article is to introduce the early Chinese clinical experience of using extracorporeal focused ultrasound (US) surgery (FUS) for the treatment of solid tumors. From December 1997 to October 2001, a total of 1038 patients with solid tumors underwent FUS ablation in 10 Chinese hospitals. The tumors included primary and metastatic liver cancer, malignant bone tumors, breast cancer, soft tissue sarcomas, kidney cancer, pancreatic cancer, abdominal and pelvic malignant tumors, uterine myoma, benign breast tumors, hepatic hemangioma and other solid tumors. In this article, pathologic changes in tumors treated with FUS, real-time diagnostic imaging for targeting, monitoring and assessment of results by follow-up images are presented. Early clinical results and complications of the technique are also reported.

Wu, F. Wang, Z.B., et al. (2004). "Circulating tumor cells in patients with solid malignancy treated by high-intensity focused ultrasound." *Ultrasound Med Biol*; 30(4): 511–517.

Abstract—The theoretical possibility that exposure of a solid malignancy to high-intensity focused ultrasound (US), or HIFU, could lead to an increased rate of metastasis still remains. Using reverse transcriptase polymerase chain reaction (RT-PCR), the potential risk of hematogenous dissemination was assessed in HIFU-treated patients with solid malignancy. RT-PCR can demonstrate the presence or absence of specific RNA fragments. On the day before HIFU ablation, 5-mL peripheral blood samples were collected, and again 5 to 7 days after HIFU, from 26 enrolled patients (hepatocellular carcinoma, HCC: 10; osteosarcoma: 16). Total RNA was isolated and RT-PCR was performed to analyze the mRNA expression of α -fetoprotein (AFP) and bone-specific alkaline phosphatase (BALP) genes. Positive AFP mRNA expression was preoperatively detected

in 8 of 10 patients with HCC. In the postoperative specimens, positive expression was also detected in 8 of 10 patients. In 2 patients, circulating tumor cells were found preoperatively, but not postoperatively. Conversely, 2 patients with no circulating tumor cells preoperatively were found to have circulating tumor cells after HIFU. Of 16 osteosarcoma patients, 12 patients had circulating tumor cells and 4 had none. After HIFU treatment, 2 of the 12 patients had converted from presence to absence of circulating cells and the remaining 4 patients remained negative. It is concluded that patients undergoing complete HIFU ablation may demonstrate conversion from presence to absence of circulating tumor-specific marker mRNA, and that HIFU would not enhance the potential risk of metastasis in patients with malignant diseases.

Wu, F. Wang, Z.B., et al. (2004). "Activated anti-tumor immunity in cancer patients after high intensity focused ultrasound ablation." *Ultrasound Med Biol*; 30(9):1217-22.

T cell-mediated immune responses represent the main cellular antitumor immunity in cancer patients. Recent studies have shown that both surgical procedure and radiation therapy could cause the functional suppression of lymphocyte-mediated cellular immunity. The purpose of current study is to evaluate whether high intensity focused ultrasound (HIFU) might change a systemic antitumor immunity, particularly T lymphocyte-mediated immunity in cancer patients. A total of 16 patients with solid malignancies were treated with HIFU. Among them, six patients had osteosarcoma (Enneking stage, II(B)4, III(B) 2), five had hepatocellular carcinoma (TNM stage, III 3, IV 2), and five had renal cell carcinoma (TNM stage, III 2, IV 3). Using flow cytometry technique, T lymphocyte and subset, B lymphocyte and natural killer cell (NK) in the peripheral blood were measured in these patients on the day before HIFU and 7 to 10 d after HIFU. The statistical significance of any observed difference is evaluated by Student's t-test. The results showed a significance increase in the population of CD4(+) lymphocytes ($p < 0.01$) and the ratio of CD4(+) /CD8(+) ($p < 0.05$) in the circulation of cancer patients after HIFU treatment. The abnormal levels of CD3(+) lymphocytes returned toward the normal range in two patients, CD4(+)/CD8(+) ratio in 3, CD19(+) lymphocytes in one and cytotoxic NK in one, respectively, in comparison to control values. It is concluded that HIFU could enhance a systemic antitumor cellular immunity in addition to local tumor destruction in patients with solid malignancies.

LIVER

Kennedy, J. E., G. R. Ter Haar, et al. (2004). "Contrast-enhanced ultrasound assessment of tissue response to high-intensity focused ultrasound." *Ultrasound Med Biol* 30(6): 851-4.

We report the use of contrast-enhanced ultrasonography as an immediate means of assessing the clinical response to high-intensity focused ultrasound (US) or HIFU treatment of liver tumours. HIFU is a noninvasive transcutaneous technique for the ablation of tumours that has been shown to destroy tumour vasculature, as well as to cause coagulative necrosis of tumour cells. As a dynamic indicator of tissue perfusion, microbubble contrast agents have already been reported to increase the diagnostic sensitivity of ultrasonography in the detection of liver tumours. This report documents the ability of one IV microbubble contrast agent (SonoVue(R), Bracco, Italy) to delineate the extent of HIFU ablation by comparison of pre- and immediately posttreatment perfusion within the target tumour. Observed changes were seen to correlate well with the ablated volume on histologic evaluation of the treated volume. This is the first time that this imaging technique has been reported in this setting.

Kennedy, J. E., F. Wu, et al. (2004). "High-intensity focused ultrasound for the treatment of liver tumours." *Ultrasonics* 42(1-9): 931-5.

High-intensity focused ultrasound (HIFU) has been investigated as a tool for the treatment of cancer for many decades, but is only now beginning to emerge as a potential alternative to conventional therapies. In recent years, clinical trials have evaluated the clinical efficacy of a number of devices worldwide. In Oxford, UK, we have been using the JC HIFU system (HAIFU Technology Company, Chongqing, PR China) in clinical trials since November 2002. This is the first report of its clinical use outside mainland China. The device is non-invasive, and employs an extracorporeal transducer operating at 0.8-1.6 MHz (aperture 12-15 cm, focal length 9-15 cm), operating clinically at [Formula: see text] (free field) of 5-15 KWcm(-2). The aims of the trials are to evaluate the safety and performance of the device. Performance is being evaluated through two parallel protocols. One employs radiological assessment of response with the use of follow-up magnetic resonance imaging and microbubble-contrast ultrasound. In the other, histological assessment will be made following elective surgical resection of the HIFU treated tumours. Eleven patients with liver tumours have been treated with HIFU to date. Adverse events include transient pain and minor skin burns. Observed response from the various assessment modalities is discussed.

Wu, F. Wang, Z.B., et al. (2004). "Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma." *Ann Surg Oncol*; 11(12):1061-9.

BACKGROUND: High intensity focused ultrasound (HIFU) is a noninvasive treatment modality that induces complete coagulative necrosis of a deep tumor through the intact skin. The current study was conducted to determine the safety, efficacy, and feasibility of extracorporeal HIFU in the treatment of patients with hepatocellular carcinoma (HCC). METHODS: A total of 55 patients with HCC with cirrhosis were enrolled in this prospective, nonrandomized clinical trial. Among them, 51 patients had unresectable HCC. Tumor size ranged from 4 to 14 cm in diameter with mean diameter of 8.14 cm. According to tumor, node, metastasis (TNM) classification, 15 patients corresponded to stage II, 16 to stage IIIA, and 24 to IIIC. All patients had HIFU, and the median number of HIFU session was 1.69. Safety and efficacy of HIFU were assessed in this trial. RESULTS: No severe side effect was observed in the patients treated with HIFU. Follow-up imaging showed an absence of tumor vascular supply and the shrinkage of treated lesions. Serum alpha-fetoprotein returned to normal level in 34% of patients. The overall survival rates at 6, 12, and 18 months were 86.1%, 61.5%, and 35.3%, respectively. The survival rates were significantly higher in patients in stage II than those in stage IIIA ($P = .0132$) and in stage IIIC ($P = .0265$). CONCLUSION: As a noninvasive therapy, HIFU appears to be effective, safe, and feasible in the treatment of patients with HCC. It may play an important role in the ablation of large tumors.

Wu, F, Z. B. Wang, et al. (2005). "Advanced hepatocellular carcinoma: treatment with high-intensity focused ultrasound ablation combined with transcatheter arterial embolization." *Radiology*; 235(2):659-67.

PURPOSE: To evaluate ultrasonographically (US)-guided high-intensity focused ultrasound ablation combined with transcatheter arterial chemoembolization (TACE) in the treatment of stage IVA hepatocellular carcinoma (HCC). MATERIALS AND METHODS: Institutional review board approval and informed consent were obtained. From November 1998 to May 2000, 50 consecutive patients with stage IVA HCC (TNM classification, T4N0-1M0) were alternately enrolled in one of two treatment groups: group 1 ($n = 26$), in which TACE was performed alone, and group 2 ($n = 24$), in which transcatheter ablation of HCC with high-intensity focused ultrasound was performed 2-4 weeks after TACE. The tumors were 4-14 cm in diameter (mean, 10.5 cm). Immediate therapeutic effects were assessed at follow-up with Doppler US and computed tomography or magnetic resonance imaging. All patients were followed up for 3-24 months (mean, 8

months) to observe long-term therapeutic effects and complications in both groups. Tumor reduction rates, median survival time, and cumulative survival rates in both groups were calculated by using the unpaired Student t test and Kaplan-Meier method. RESULTS: No severe complication was observed after focused ultrasound ablation, and no unexpected side effects were noted after TACE. Follow-up images showed absence or reduction of blood supply in the lesions after focused ultrasound ablation when compared with blood supply after TACE alone. The median survival time was 11.3 months in group 2 and 4.0 months in group 1 ($P = .004$). The 6-month survival rate was 80.4%-85.4% in group 2 and 13.2% in group 1 ($P = .002$), and the 1-year survival rate was 42.9% and 0%, respectively. Median reductions in tumor size as a percentage of initial tumor volume at 1, 3, 6, and 12 months after treatment, respectively, were 28.6%, 35.0%, 50.0%, and 50.0% in group 2 and 4.8%, 7.7%, 10.0%, and 0% in group 1 ($P < .01$). CONCLUSION: The combination of high-intensity focused ultrasound ablation and TACE is a promising approach in patients with advanced-stage HCC, but large-scale randomized clinical trials are necessary for confirmation.

KIDNEY

Kohrmann, K. U., M. S. Michel, et al. (2002). "High intensity focused ultrasound as noninvasive therapy for multilocal renal cell carcinoma: case study and review of the literature." J Urol 167(6): 2397-403.

PURPOSE: Noninvasive tumor ablation can be achieved by extracorporeally induced high intensity focused ultrasound. Clinical high intensity focused ultrasound performed to date for renal tumors have only been experimental in nature. We present specific details on a patient with renal cell carcinoma who underwent high intensity focused ultrasound with curative intent and long-term followup examinations. MATERIALS AND METHODS: Ultrasound waves were generated by a cylindrical piezoelectric element focused by a paraboloid reflector. High intensity focused ultrasound was applied to 3 tumors in 3 sessions with the patient under general anesthesia or sedation analgesia, followed by magnetic resonance imaging for 6 months. RESULTS: After treatment magnetic resonance imaging showed necrosis in the 2 tumors in the lower kidney pole within 17 and 48 days, respectively. The necrotic tumor area shrank thereafter within 6 months. The tumor in the upper pole was not affected by treatment due to absorption of the ultrasound energy by the interposed ribs. General anesthesia was required to apply high energy levels of focused ultrasound. Absorption of high

intensity focused ultrasound in the tissue induced sharply demarcated thermonecrosis. For 50 years patients have been treated with high intensity focused ultrasound for different indications, focusing on the brain, eyes, prostate, liver and bladder. For the kidney experimental but only few clinical studies indicate sufficient tissue ablation. CONCLUSIONS: In our case contactless noninvasive application of high intensity focused ultrasound to 2 renal carcinomas achieved thermal ablation. When high intensity focused ultrasound energy was coupled correctly, no lesions occurred outside of the target area. Successful high intensity focused ultrasound application depended on optimum energy coupling, a sufficiently high ultrasound energy level and general anesthesia.

Wu, F., Z. B. Wang, et al. (2003). "Preliminary experience using high intensity focused ultrasound for the treatment of patients with advanced stage renal malignancy." J Urol 170(6 Pt 1): 2237-40.

PURPOSE: We present the preliminary results of patients with advanced stage renal malignancy treated with high intensity focused ultrasound (HIFU), and investigate the safety and feasibility of using HIFU in the treatment of selected patients with renal tumors. MATERIALS AND METHODS: HIFU treatment was performed in 12 patients with advanced stage renal cell carcinoma and 1 patient with colon cancer metastasized to kidney. Patients were followed after treatment to observe complications and long-term therapeutic efficacy. Complications and changes in symptoms seen at presentation were recorded. Mid stream urine specimens were sent for microscopy and serum creatinine was measured postoperatively. Followup radiological examinations were performed to detect tumor response to the ablation. RESULTS: A total of 13 patients received HIFU treatment safely, including 10 who had partial ablation and 3 who had complete tumor ablation. After HIFU hematuria disappeared in 7 of 8 patients and flank pain of presumed malignant origin disappeared in 9 of 10 patients. Postoperative images showed decrease in or absence of tumor blood supply in the treated region and significant shrinkage of the ablated tumor. Of the 13 patients 7 died (median survival 14.1 months, range 2 to 27) and 6 were still alive with median followup of 18.5 months (range 10 to 27). CONCLUSIONS: This preliminary experience suggests that HIFU could be safe and feasible in the treatment of patients with advanced renal malignancy.

BREAST

Hynnen, K., O. Pomeroy, et al. (2001). "MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: a feasibility study." *Radiology* 219(1): 176-185.

PURPOSE: To test the feasibility of noninvasive magnetic resonance (MR) imaging-guided focused ultrasound surgery (FUS) of benign fibroadenomas in the breast. MATERIALS AND METHODS: Eleven fibroadenomas in nine patients under local anesthesia were treated with MR imaging-guided FUS. Based on a T2-weighted definition of target volumes, sequential sonications were delivered to treat the entire target. Temperature-sensitive phase-difference-based MR imaging was performed during each sonication to monitor focus localization and tissue temperature changes. After the procedure, T2-weighted and contrast material-enhanced T1-weighted MR imaging were performed to evaluate immediate and long-term effects. RESULTS: Thermal imaging sequences were improved over the treatment period, with 82% (279 of 342) of the hot spots visible in the last seven treatments. The MR imager was used to measure temperature elevation (12.8 degrees -49.9 degrees C) from these treatments. Eight of the 11 lesions treated demonstrated complete or partial lack of contrast material uptake on posttherapy T1-weighted images. Three lesions showed no marked decrease of contrast material uptake. This lack of effective treatment was most likely due to a lower acoustic power and/or patient movement that caused misregistration. No adverse effects were detected, except for one case of transient edema in the pectoralis muscle 2 days after therapy. CONCLUSION: MR imaging-guided FUS can be performed to noninvasively coagulate benign breast fibroadenomas.

Gianfelice, D., A. Khat, et al. (2003). "MR imaging-guided focused US ablation of breast cancer: histopathologic assessment of effectiveness-- initial experience." *Radiology* 227(3): 849-55.

PURPOSE: To evaluate the effectiveness of noninvasive magnetic resonance (MR) imaging-guided focused ultrasonographic (US) ablation of breast carcinomas. MATERIALS AND METHODS: Before undergoing tumor resection, 12 patients with invasive breast carcinomas were treated with MR imaging-guided focused US ablation consisting of multiple sonications of targeted points that were monitored with temperature-sensitive MR imaging. The patients were treated with either one of two focused US systems. The effectiveness of the treatment was determined at histopathologic analysis of the resected mass that was performed to determine the volumes of necrosed and residual tumor. Complications resulting from the procedure were assessed by

means of questionnaires, medical examinations, and MR image analysis. RESULTS: US ablation was well tolerated by the patients, and with the exception of minor skin burns in two patients, no complications occurred. Histopathologic analysis of resected tumor sections enabled quantification of the amount of necrosed and residual tumor and visualization of the surrounding hemorrhage. In three patients treated with one of the US systems, a mean of 46.7% of the tumor was within the targeted zone and a mean of 43.3% of the cancer tissue was necrosed. In nine patients treated with the other US system, a mean of 95.6% of the tumor was within the targeted zone and a mean of 88.3% of the cancer tissue was necrosed. Residual tumor was identified predominantly at the periphery of the tumor mass; this indicated the need to increase the total targeted area (ie, with an increased number of sonications). CONCLUSION: Thermal coagulation of small breast tumors by means of MR imaging-guided focused US appears to be a promising noninvasive ablation procedure.

Gianfelice, D., A. Khiat, et al. (2003). "MR imaging-guided focused ultrasound surgery of breast cancer: correlation of dynamic contrast-enhanced MRI with histopathologic findings." *Breast Cancer Res Treat*; 82(2):93-101.

PURPOSE: To assess the value of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) parameters to monitor residual tumor following non-invasive MRI-guided focused ultrasound surgery (MRIGFUS) of breast tumors. METHODS: DCE-MRI data were acquired before and after the MRIGFUS treatment of small breast tumors ($d < 3.5$ cm) for 17 patients. The lesion was surgically resected and the presence of residual tumor was determined by histopathological analysis. The percentage of residual tumor was correlated with three DCE-MRI parameters measured at the maximally enhancing site of each tumor: increase in signal intensity (ISI), maximum difference function (MDF) and positive enhancement integral (PEI). RESULTS: A good correlation was found between the ISI ($r = 0.897$), MDF ($r = 0.789$) and PEI ($r = 0.859$) parameters and the percentage of residual viable tumor determined by histopathology. A receiver operator characteristic curve analysis yielded a cutoff value for ISI at 20% with a sensitivity of 77% and a specificity of 100%. CONCLUSION: These results suggest that parameters from DCE-MRI data could provide a reliable non-invasive method for assessing residual tumor following MRIGFUS treatment of breast tumors.

Wu, F., Z. B. Wang, et al. (2003). "Changes in biologic characteristics of breast cancer treated with high-intensity focused ultrasound." *Ultrasound Med Biol* 29(10): 1487-92.

Proliferation, invasion, immortalization and metastasis are the main malignant characteristics of cancer. Previous studies have shown that high-intensity focused ultrasound (US), or HIFU, can induce irreversible damage both to breast cancer cells and to tumor blood vessels. However, light microscopy alone may not always show this clearly. In this study, molecular biologic techniques were used to examine any changes in molecular markers associated with malignant behavior after exposure to HIFU. A total of 48 women with breast cancer were randomized to a control group (mastectomy) and a HIFU group (HIFU followed by mastectomy).

Immunohistochemical staining, messenger RNA (mRNA) in situ hybridization and telomere-repeat amplification protocol-enzyme-linked immunosorbent assay (TRAP-ELISA) techniques were used to detect tumor expression of proliferating cell nuclear antigen (PCNA), cell adhesion molecule CD44v6, matrix metalloproteinase-9 (MMP-9), erbB2 mRNA, and to measure telomerase activity in both groups. The results demonstrated that there were significant alterations in expression of PCNA, CD44v6, MMP-9, erbB2 mRNA, and a dramatic decrease in telomerase activity in the HIFU group. It is concluded that malignant tumor characteristics are arrested by HIFU, and that biologic factors are potential markers for assessing HIFU efficacy.

Wu, F., Z. B. Wang, et al. (2003). "A randomised clinical trial of high-intensity focused ultrasound ablation for the treatment of patients with localised breast cancer." *Br J Cancer* 89(12): 2227-33.

High-intensity focused ultrasound (HIFU) is a noninvasive treatment that induces complete coagulative necrosis of a tumour at depth through the intact skin. This study was to explore the possibility of using HIFU for the treatment of patients with localised breast cancer in a controlled clinical trial. A total of 48 women with biopsy-proven breast cancer (T(1-2), N(0-2), M0) were randomised to the control group in which modified radical mastectomy was performed, and the HIFU group in which an extracorporeal HIFU ablation of breast cancer was followed by modified radical mastectomy. Short-term follow-up, pathologic and immunohistochemical stains were performed to assess the therapeutic effects on tumour and complications of HIFU. The results showed that no severe side effect was observed in the HIFU-treated patients. Pathologic findings revealed that HIFU-treated tumour cells underwent complete coagulative necrosis, and tumour vascular vessels were severely damaged. Immunohistochemical staining showed that no expression of PCNA, MMP-9, and CD44v6 was detected within the treated tumour cells in the HIFU group, indicating that the treated tumour cells lost the abilities of proliferation, invasion, and metastasis. It is concluded that, as a noninvasive therapy, HIFU could be effective, safe, and feasible in the extracorporeal treatment of localised breast cancer.

Wu, F. Wang, Z.B., et al. (2005). "Extracorporeal high intensity focused ultrasound treatment for patients with breast cancer". *Breast Cancer Research and Treatment* 92: 51–60.

Purpose. To investigate the safety, efficacy and feasibility of using high-intensity focused ultrasound (HIFU) as a non-invasive treatment for patients with breast cancer. Patients and Methods. Twenty-two patients with breast cancer were enrolled into this non-randomized prospective trial. Disease TNM stage was classified as stage I in 4 patients, stage IIA in 9 patients, stage IIB in 8 patients, and stage IV in 1 patient. Tumor size ranged from 2 to 4.8 cm in diameter (mean 3.4 cm). All patients received chemotherapy, radiation and tamoxifen, following HIFU for the primary lesions. Outcome measures included radiological and pathologic assessment of the treated tumor, cosmesis, and local recurrence. A cumulative survival rate is calculated by using the Kaplan–Meier method. Results. No severe complications were encountered after HIFU. Post-operative imaging demonstrated positive response and regression of all treated lesions. Follow-up biopsy revealed coagulation necrosis of target tumor and subsequent replacement by fibroblastic tissue. After a median follow-up of 54.8 months, 1 patient died, 1 was lost to follow-up, and 20 were still alive. Two of 22 patients developed local recurrence. Five-year disease-free survival and recurrence-free survival were 95% and 89%, respectively. Cosmetic result was judged as good to excellent in 94% of patients. Conclusions. HIFU treatment is safe, effective, and feasible for patients with breast cancer. But, large-scale, multiple-center clinical trials will be needed to determine the future role of this novel modality.

UTERINE FIBROIDS

Stewart, E. A., W. M. Gedroyc, et al. (2003). "Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique." *Am J Obstet Gynecol* 189(1): 48-54.

OBJECTIVE: The purpose of this study was to determine the safety and efficacy of focused ultrasound surgery with magnetic resonance imaging guidance for the noninvasive treatment of uterine leiomyomas. STUDY DESIGN: Fifty-five women with clinically significant uterine leiomyomas were treated. Pain and complications were assessed prospectively, and posttreatment magnetic resonance imaging was used to measure the treatment effects. Patients in three of the five centers underwent planned hysterectomy after treatment, which provided pathologic correlation of treatment. RESULTS: Seventy-six percent of the enrolled patients completed the full treatment session. All treatments were conducted in an outpatient setting with minimal discomfort for

subjects and no major complications. Pathologic examination of the uterus confirmed that magnetic resonance imaging guidance provides the safe and accurate delivery of effective levels of thermal energy with a 3-fold increase in volume of histologically documented necrosis, compared with treatment volume (6.6 0.8 vs 18.4 3.9 mL, $P < .005$). CONCLUSION: Magnetic resonance imaging-guided focused ultrasound surgery appears to be a well-tolerated treatment for uterine leiomyomas.

BONE

Wu, F., Wang, Z.B., et al. (2003). Non-invasive ablation of high intensity focused ultrasound for the treatment of patients with malignant bone tumours. J Bone Joint Surg (Br) 87-B; Issue Supp I, 4.

Purpose of study: To investigate the safety, efficacy, and feasibility of using high intensity focused ultrasound (HIFU) for the treatment of malignant bone tumors. Methods: Forty-four patients with biopsy-proven malignant bone tumors were treated with HIFU (osteosarcoma: 32; chondrosarcoma: 3; periosteal osteosarcoma: 2; Ewing sarcoma: 1; other malignant bone tumor: 3, and unclassified tumor: 2). These tumors were situated as follows: distal femur – 20; proximal tibia – 7; mid-shaft of femur – 6; ilium – 2; shaft of fibula – 2; other – 4. HIFU was given as a noninvasive limb-salvage treatment in combination with neoadjuvant chemotherapy (methotrexate, adriamycin, cisplatin and ifosfamide) in thirty-four patients (Enneking's Stage_b). Ten patients with stage IIIb (9 patients with lung metastasis) were treated with HIFU alone with palliative intent. The largest dimension of the tumors ranged from 5 to 46 cm. Postoperative biopsy, follow-up imaging (DSA, CT or MRI, and ECT), and functional evaluation were performed, and median survival time was calculated using the Kaplan-Meier method. Results: Histopathological examination demonstrated clear evidence of tumor destruction and regrowth of normal bone in the treated region. When compared with baseline, follow-up imaging indicated complete coagulative necrosis of the treated tumors. Enneking's functional scores were >20 , 15–20, and <15 in 20, 14 and 5 cases respectively. Median follow-up was 23 months (range 10 to 40 months). Total survival rate was 85% (38/44). One patient with stage_b disease, and 5 patients with stage IIIb disease died as a result of distant metastases after HIFU treatment. 5 patients underwent amputation after local recurrence. Few complications were observed during follow-up. These were limited to 3 pathological fractures, 2 cases of peripheral nerve damage, restricted joint movement in 1 case, and epiphyseal separation in 1 case. Conclusions: HIFU is safe, effective, and feasible in the treatment of patients with malignant bone tumors.

PANCREAS

Wang, X., Sun, J. (2002) "High-intensity focused ultrasound in patients with late-stage pancreatic carcinoma." Chin Med J (Engl); 115(9):1332-5.

OBJECTIVES: To observe the efficacy of high intensity focused ultrasound (HIFU) in the treatment of late-stage pancreatic carcinoma and evaluate its influence on cell-mediated immunity in the host. METHODS: Fifteen patients with late-stage pancreatic carcinoma had their tumor tissue completely destroyed with HIFU. Evaluation of efficacy was made on the basis of clinical symptom changes, variations in tumor echo, changes in pancreatic amylase, serum CA19-9 and CA242, CD3(+), CD4(+) subsets, CD4(+)/CD8(+) ratios and NK cell activity. RESULTS: Clinical symptoms such as pain were significantly alleviated, echo of tumor was enhanced with B-US, CA19-9 and CA242 were decreased and pancreatic amylase showed no change. Eating, sleeping and mental status were all markedly improved; no serious complications were seen. On the other hand, NK cell activity was significantly enhanced in 10 patients ($P < 0.05$), and CD3(+) and CD4(+) subsets as well as CD4(+)/CD8(+) ratios increased to different degrees. CONCLUSIONS: The use of HIFU in the treatment of late-stage pancreatic carcinoma is feasible and safe. It is effective in destroying the carcinoma and alleviating abdominal pain; it may enhance cell-mediated immunity in the host. This technique may offer a noninvasive therapy for the treatment of late-stage pancreatic carcinoma.