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The Role of Pulsed High Intensity Focused Ultrasound (pHIFU) in Cancer Therapy

Fox Chase Cancer Center

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Background of the Studies

- Exablate 2000 HIFU system installed in the Dept of Rad Onc at FCCC in 2006

- Orthotopic prostate tumor model was developed in our laboratory

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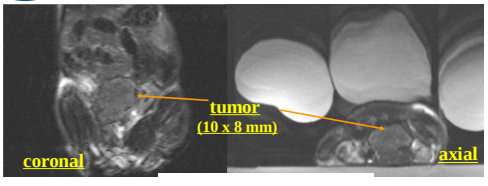
Prostate Tumor in Mouse



T2-weighted MRI (1.5T)
Resolution: 0.23 mm

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Motivation

- **Hypothesis**

pHIFU exposures enhances drug delivery and increases the efficacy of gene/chemotherapy in inhibiting prostate cancer growth *in vivo*, particularly when combined with AD (androgen deprivation) or RT.

- **Purpose of the study**

To verify the concept of enhancing drug uptake with MR guided pHIFU.

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Motivation of Targeted Drug Delivery Studies

- pHIFU → short waves → ↑vascular or cell membrane permeability → ↑drug concentration in target
- MR used to place ultrasonic beam in the target and monitoring the effect of treatment in real time
- Enhancement of gene/chemotherapy in prostate cancer + Androgen deprivation +RT → ↑prostate cure rate

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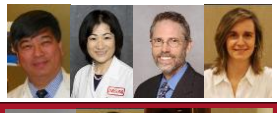
HIFU Research Team



Charlie Ma, Lili Chen, Alan Pollack, Dusica Cvetkovic, Zhaomei Mu, Xiaoming Chen, Bin Wang, Roohi Gupta

Pilot Study (1) Doxorubicin

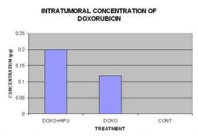


Figure 4 Comparison of the doxorubicin concentration in tumors with and without HIFU treatment. SD is 0.02 with HIFU and 0.025 without HIFU, respectively.

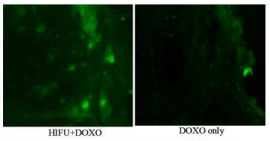


Figure 5 Comparison of the doxorubicin distribution with and without HIFU treatment.

Parameters: 1 MHz; 4 W of acoustic power and 5 Hz frequency with 50% duty cycle (0.1s power on, 0.1s power off) for 1 minute /per sonication

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Pilot study (2) Cellular uptake of AS-MDM2 with MRgHIFU in vivo

1) MDM2 is an oncogene and overexpressed in 30-40% of prostate cancer. Antisense MDM2 oligonucleotide (AS-MDM2) inhibits MDM2 expression, and enhances the effects of radiation and chemotherapy on prostate cancer
2) The purpose of this study is to investigate the feasibility of increasing the cellular uptake of AS-MDM2 using MR guided Pulsused High Intensity Focused Ultrasound (pHIFU).

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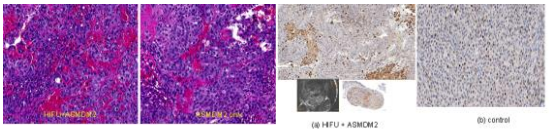
Pilot study (2) Cellular uptake of AS-MDM2 with MRgFU in vivo



H&E **(ImmunoChemistry Staining)**

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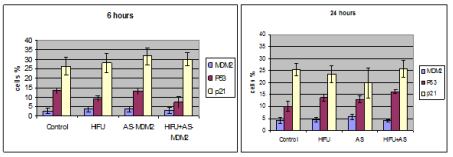
Percentage of cells showing AS-MDM2, p53 and P21 expression after IHC staining



(a) (b)

Figure 6 The percentage of cells showing MDM2, p53 and P21 expression after immunohistochemical staining with MDM2 (1:400 concentration), P53 (1:500 concentration) and P21 (1:4000 concentration).

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Intratumoral uptake of [^{3}H]-docetaxel in vivo using MRgHIFU

- The purpose of the study
  - if the delivery of ^{3}H-docetaxel is enhanced in the treated prostate tumor then the insignificant results from the gene therapy experiments would be due to the ineffectiveness of the gene drug
- The rational of selection of Docetaxel

1. Routinely used in clinic
2. A potent radio-sensitizer: used for quantitative measurement

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Study Design

- LNCaP 10^6, were grown orthotopically in the prostates of mice
- Three groups: 1) pHIFU+ ^{3}H-docetaxel, 2) ^{3}H-docetaxel alone, 3) control
- Use the same treatment pHIFU parameters as for gene therapy
- ^{3}H-docetaxel (1.25 µci/25 g) received by tail vein immediately after pHIFU.
- Animals euthanized 30 minutes post treatment and the ^{3}H-docetaxel were measured quantitatively (cmp counts) using a scintillation detector

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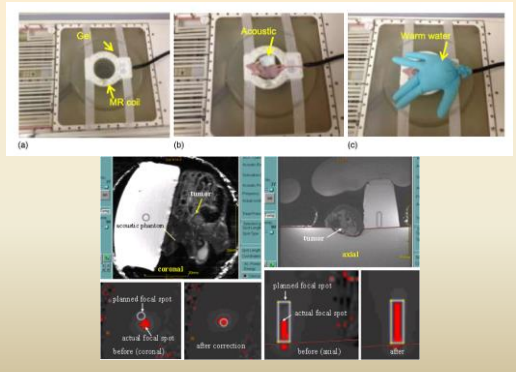
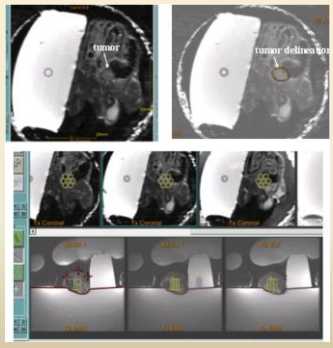
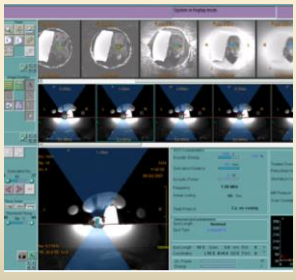
Animal Setup and Focal Spot Calibration



Treatment Planning in Real Time



Real Time Monitoring



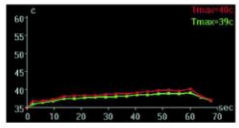
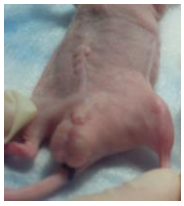


FIG. 3. Real-time temperature measurement with MR thermometry during animal sonication (top red line: maximum temperature measured at the focal spot in a single voxel of 0.86 × 1.72 × 3.00 mm; bottom green line: average temperature measured over 3 voxels). The ambient temperature was set to 35 °C, which was the typical mouse body temperature in the beginning of the sonication period.

Results

- No skin damage
- No death of animals during or after the pHIFU treatment



← Immediately after pHIFU

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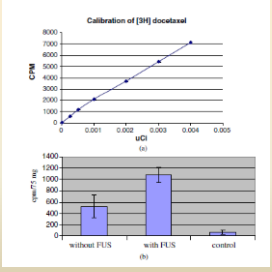
Comparison of ^{3}H-docetaxel in Tumor with and without pHIFU



P=0.037

Chen et all. Phys. Med. Biol. 55 (2010) 7399–7410

Quantitative study of Enhancement of Doxorubicin Delivery in Prostate Cancer *in vivo* with MRgHIFU

- **"Optimal" treatment parameters**
  - *1 MHz, 25 W acoustic power, and 1 Hz pulse rate with a 10% duty cycle for 60 s for each spot.*
- **Temperature elevations**
  <5 °C observed during the treatment,

Chen X et al. Med. Phys. 39 (5), (2012)2780-86

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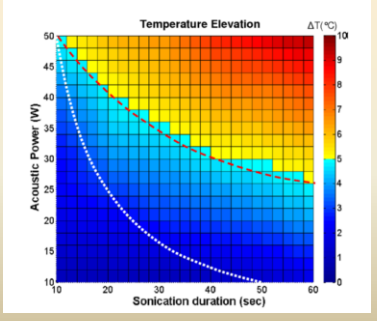
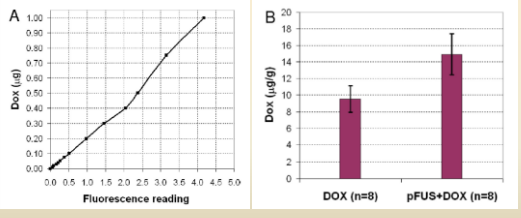
Relationship of Acoustic Power, Sonication Durations and Temperature Elevation



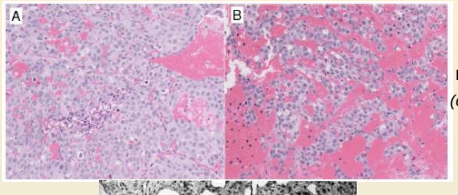
Results

Comparison of Dox with and without pHIFU

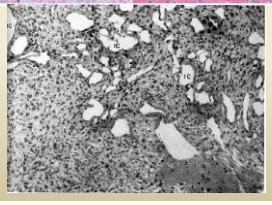


P=0.05

Histological Analysis

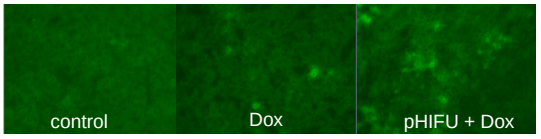


non-thermal
(current study)



"implosion cysts"
Thermal damage
Chen et al. 1993. UMB

Dox Distribution in Prostate Tumor after pHIFU



X 20

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Evaluation of the Efficacy of the Enhancement of Docetaxel by pHIFU for Prostate Treatment

1) Docetaxel + pHIFU in tumor growth control
2) Docetaxel +pHIFU +RT in tumor growth control
3) pHIFU + RT using "optimal" pHIFU parameters and tumor sizes
4) pHIFU alone for tumor growth control

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Study (1) - Study Design

- Tumor volume: 45 ± 9 mm^3 measured on MRI
- 4 Groups (n=5)
  (1) pHIFU alone
  (2) docetaxel + pHIFU
  (3) docetaxel alone
  (4) Control

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Study (1) - Study design
(continued)

Groups 1 and 2 = pHIFU/week x 2
Groups 2 and 3 = docetaxel by i.v. 10 mg/ kg/week x 2
Group 2 i.v injection immediately after pHIFU

- pHIFU parameters: 1MHz; 5W, 50% duty cycle (0.1 s power on and 0.1 s power off) for 60 s per sonication

- Tumor volume measured on MR (1.5T) weekly for 4 weeks

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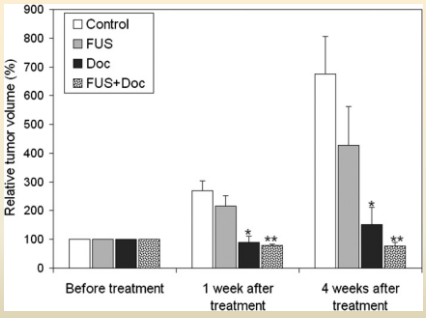
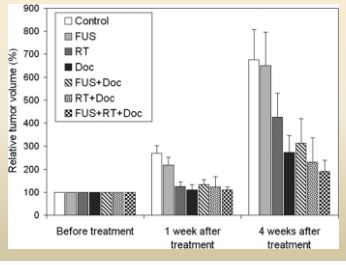
Results



Mu et al. Phys. Med. Biol. 57 (2012) 535–545

Study (2)

- Redused docetaxel dose from 10 mg/kg to 5 mg/kg for one injection)
- pHIFU treatment also for one time TX with the same parameters



Study (3)

Purpose: Evaluation of the Therapeutic Effects of pHIFU + RT

1. Using “optimal” pHIFU treatment parameters
2. RT dose: 2 Gy (Siemens Artiste linear accelerator)

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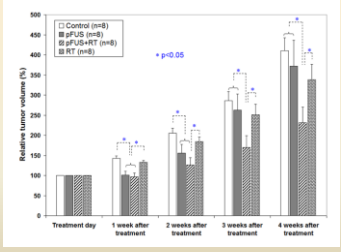
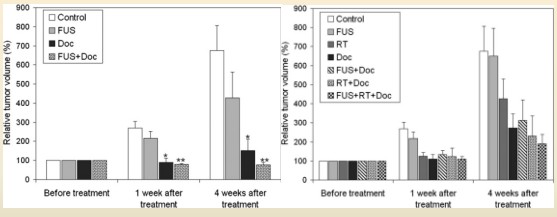
Results



Chen X et al. Medical Physics 39(6): 3899, 2012

Tumor Growth Control



pHIFU parameters:1MHz; 5W for 60 s with 50% duty cycle (0.1 s power on and 0.1 s power off) per sonication

Study (4) Therapeutic Effect of pHIFU Alone

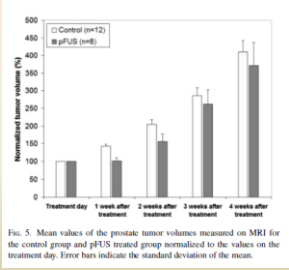
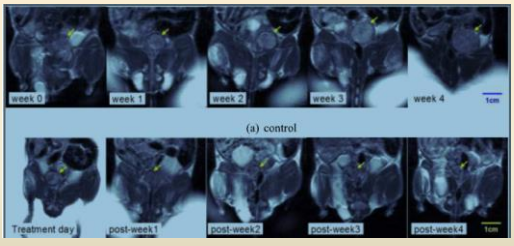


FIG. 5. Mean values of the prostate tumor volumes measured on MRI for the control group and pFUS treated group normalized to the values on the treatment day. Error bars indicate the standard deviation of the mean.

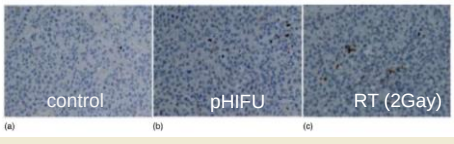
Ma et al. Med. Phys. 41 (2014) 122901-1-9

Therapeutic Effect of pHIFU on Tumor Growth



Ma et al. Med. Phys. 41 (2014) 122901-1-9

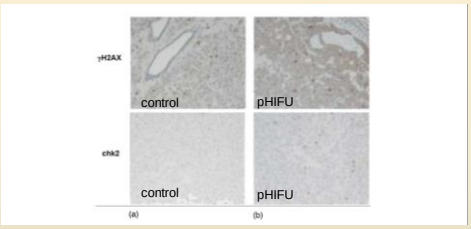
ImmunoChemical Staining-Caspase to detect apoptotic cells 24 h after treatment



The apoptosis induced by pHIFU is comparable to that by 2 Gy irradiation

Ma et al. Med. Phys. 41 (2014) 122901-1-9

ImmunoChemical Staining- γH2AX and Chk2 indicating DNA damage



48 h after treatment, the two biomarkers are in creased in the HIFU treated mice compared with the control group.

Ma et al. Med. Phys. 41 (2014) 122901-1-9

Conclusions/discussions

- Animal studies demonstrated the effectiveness of enhancement of chemotherapy by pHIFU in combination with RT for prostate tumor control *in vivo*
- The therapeutic effect of pHIFU alone may be clinically significant.

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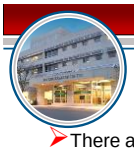

Conclusions/discussions

- There appeared to be an earlier treatment response to pHIFU than to RT, indicating different cell killing mechanisms between the two modalities.
- There was a tendency toward accelerated tumor growth in pHIFU treated tumors compared to the control mice.
- The therapeutic effect of pHIFU may be a combined result from mitotic, apoptotic, and necrotic cell death due to biophysical and biochemical reactions mediated by pHIFU with different components of the tumor cell including DNA, cell membrane, mitochondria, etc.

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Future Work

Further experiments are warranted to understand the cell killing mechanisms of pHIFU and to derive optimal ultrasound parameters and fractionation schemes to maximize the therapeutic effect of pHIFU.

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