Clinical Applications of Extracorporeal HIFU in the Treatment of Liver Malignancies

Feng Wu, MD, PhD
Steps in the R & D of a Medical Device for Therapy

◆ Design and Construct a Prototype (Key Technologies)
◆ Studies *in vitro* & *in vivo* from Small to Large Animals Using the Prototype
◆ Improvements in the Prototype for Clinical Trials
◆ Clinical Trials
◆ A Better Device (“Medical Robot”)
◆ ?…….
Key Technologies of the HIFU Device

◆ Small focus with homogeneous distribution of high-intensity US energy
◆ How to move HIFU small focus for complete ablation of a targeted tumour
◆ Image-guided therapy procedure
Target organ (e.g. liver)

‘Lesion’ of coagulation necrosis at focus

Skin

Transducer

Undamaged tissue in front of focus
3D HIFU therapeutic plan

One HIFU pulse exposure

Multiple-pulse Scanning beam

Treatment planning

Volume

Treatment plan

Slice
Image Guidance

◆ Planning
◆ Targeting
◆ Monitoring
◆ Controlling
◆ Assessing tumour response
Image Guidance

- Ultrasonography (US imaging)
  Hyperechoic changes within ablated tissue
- Magnetic resonance imaging (MRI)
  Temperature measurement within ablated tissue
Transducer
- Plane transducer with integral aluminium lens (choice of 6 with different focal lengths)

Imaging
- Built-in coaxial 3.5 MHz diagnostic transducer
- Real-time imaging of treated area
Real-time US image monitoring

Real-time visualization of coagulation necrosis in *in vivo* pig liver on the US image immediately after one-pulse HIFU exposure.
Real-time US image monitoring

Real-time visualization of coagulation necrosis in *in vivo* pig liver on the US image immediately after one linear track HIFU exposure.
Real-time visualization of coagulation necrosis in *in vivo* pig liver on the US image immediately after two-track HIFU exposure.
HIFU treatment for liver tumor
Real-time US Images during HIFU Procedure in Large HCC
Clinical Applications of Model-JC HAIFU

  1,038 patients in 10 Chinese hospitals

- Nov. 2001 - Mar. 2004
  Approx. 2,500 patients in 20 Chinese hospitals

- Churchill Hospital of Oxford University, UK
  42 patients (until April 2005)

- Clinica E. T., Japan
  67 patients (until Sep. 2004)

- Oasis Cancer Center, Busan, South Korea
  160 patients (until May, 2005)

- Honam Hospital, Gwangju, South Korea
  50 patients (until May, 2005)
Model-JC HIFU System (CE Approval)

The HIFU System Made by Chongqing Haifu (HIFU) Tech. Co., Lt., China
1,038 Patients from 1997 to 2001

Solid Malignancies

- Liver Cancer: 474 cases
- Malignant Bone Tumours: 153 cases
- Breast Cancer: 106 Cases
- Soft Tissue Sarcoma: 77 cases
- Kidney Cancer: 27 cases
- Pancreatic Cancer: 10 cases
- Abdominal Cancer: 20 cases
- Lung Cancer: 4 cases
- Others: 31 cases

Solid Benign Tumours

- Uterine Myoma: 85 cases
- Benign Breast Tumours: 28 cases
- Benign Soft Tissue Tumours: 13 cases
- Benign Liver Tumours: 4 cases
- Others: 6 cases

HIFU CLINICAL TRIALS

------HIFU Treatment

For primary liver cancer
Why do we use HIFU in primary liver cancer?

- Only 15-20% HCC patients can be cured using conventional therapies such as hepatic resection, minimally invasive ablation and liver transplantation.
- No successful therapies can be offered to 80-85% of patients with HCC until now.
Why do we use HIFU in primary liver cancer?

- Improve the quality of life in patients with end-stage HCC
- Downgrade large HCC for subsequent hepatic resection because of cirrhosis
- Establish the bridge between unresectable HCC and liver transplantation
- Non-invasive treatment for small HCC
Purposes of HIFU Clinical Trial

- **Safety**
  ---- (Phase I)

- **Effectiveness and feasibility**
  ---- (Phase II)

- **Efficacy: Long-term survival rate**
  ---- (Phase III)
Clinical Problems in HIFU ablation for HCC

- Liver motion caused by breathing
- Rib cage
- Long treatment time because of large volume tumours with rich blood supply
- HCC lesion close to diaphragm
- Skin burn because of rib cage
Liver motion problem

- General Anaesthesia
  -- Tracheal intubation
  one-lung mechanical ventilation
- Automatic tracking respiration system will be used during HIFU procedure in the future
Is it possible to treat liver lesions through the intercostal space between ribs?
Rib cage problem

Courtesy of Dr. James Kennedy
Rib cage problem

![Graph showing the relationship between normalized pressure amplitude and distance from maximum (mm) with different absorber conditions.]

Courtesy of Dr. James Kennedy
Rib cage problem

Courtesy of Dr. James Kennedy
Rib cage problem

◆ Clinical solution
  -- Remove the ribs using surgery
Rib cage problem

- Technical solution---increase US energy deposition in the focal region for liver cancer ablation
  - Make larger HIFU transducer
  - Change the shape of the transducer
  - Time-reversal phased array HIFU transducer
  - Others
Long treatment time problem

- Use controllable cavitation for increasing the volume of tissue necrosis
- Change HIFU exposure regime
  --- Linear track exposure
- Increase the US energy deposition in targeted tumours
  --- Lipiodol (iodized oil), Micro-bubbles
- Reduce tumour blood supply
  --- Arterial embolization
Lesion close to the diaphragm

Percutaneously inject 0.9% normal saline into chest cavity
Skin burn problem

- Reduce the temperature of degassed water
- Monitor skin changes on US image before and after HIFU exposures
- Decrease US energy deposition on the skin
- Pay attention to the pre-focal peak of the transducer
ASSESSMENT OF HIFU ABLATION WITH HISTOLOGICAL TECHNIQUES
10 days after treatment, coagulation necrosis was observed on macroscopic examination in the surgical specimen.

10 days after treatment, all tumor cells were damaged by HIFU within targeted HCC, HE 200 & 400 ×

Tumor vascular vessels are severely damaged by HIFU within targeted HCC, HE 400×

Elasticity fibrin Victoria and ponceau’s histochemical staining, 400 ×

Vascular elasticity fibrin and collagen fibrin at the treated region collapsed significantly, indicative of tumor vessel destruction.

ASSESSMENT OF HIFU ABLATION WITH IMAGING FOLLOW-UP
Color Doppler Ultrasound Imaging

Before HIFU

5 days after HIFU

Changes in enhanced CT images before and after HIFU treatment in a 65-year-old man with HCC

Enhanced-MRI changes in a 48-year-old patient with primary liver cancer before and after HIFU ablation

Before HIFU

Dynamic Enhanced -MR, T1WI

2 weeks after HIFU

Arterial Phase

Venous Phase

Delayed Phase
HIFU TREATMENT FOR PATIENTS WITH END-STAGE HCC
Enhanced-CT changes in a 56-year-old patient with advanced-stage liver cancer before and after HIFU.

Enhanced MRI changes in a 62-year-old patient with HCC before and 2 weeks after HIFU treatment. The tumors were located in both right and left lobes of the liver respectively.
Enhanced MRI changes in a 68-year-old patient with HCC before and 2 weeks after HIFU treatment. The tumors were located close to the diaphragm and the inferior vena cava respectively.
MR, T1WI

Before HIFU

4 months after HIFU
Enhanced-MRI, T1WI

4 months after HIFU
Randomized HIFU Clinical Trial

50 End-stage HCC Patients (TNM Stage IVA)

- TACE (26 Patients)
- TACE + HIFU (24 Patients)

# Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TACE Group</th>
<th>HIFU+TACE Group</th>
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</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>21/5</td>
<td>15/9</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>44.5 ± 8.4</td>
<td>47 ± 12.6</td>
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<tr>
<td>Mean Tumor Size (cm)</td>
<td>11.26</td>
<td>10.03</td>
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<tr>
<td>&lt;5cm/5~10cm/&gt;10cm</td>
<td>0/10/16</td>
<td>1/10/13</td>
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<tr>
<td>No. of Lesion (mean)</td>
<td>2.4</td>
<td>2.7</td>
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<tr>
<td>1 lesion</td>
<td>9</td>
<td>6</td>
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<tr>
<td>2/3/4 lesions</td>
<td>4/8/5</td>
<td>4/6/8</td>
</tr>
<tr>
<td>Hepatitis B/HBs-Ag (+)</td>
<td>18/6</td>
<td>20/4</td>
</tr>
<tr>
<td>Child-Pugh class (A/B)</td>
<td>24/2</td>
<td>24/0</td>
</tr>
<tr>
<td>Portal vein involvement</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>TNM stages (IVA)</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Position of lesion (Left/Right/Both lobes)</td>
<td>2/12/12</td>
<td>2/4/18</td>
</tr>
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</table>
Cumulative survival curves, calculated with the Kaplan-Meier method, for patients treated with either TACE alone (solid line) or TACE and HIFU ablation (dashed line).

Contrast-Enhanced MRI, T1WI

Before TACE  1 month after TACE  2 months After HIFU

Median rates of reduction in tumor size during the follow-up period for patients treated with either TACE alone or TACE and HIFU ablation.

Figure 4. Transverse contrast-enhanced CT images (nonhelical) obtained in a 58-year-old patient who underwent one course of TACE and one session of ultrasound ablation for HCC (arrowhead). Compared with tumor size before ablation, an obvious shrinkage was observed in the lesion treated with TACE plus ablation. Images were obtained (a) before TACE; (b) 3 weeks after TACE and just before ultrasound ablation; and (c) 4 weeks, (d) 6 months, (e) 1 year, and (f) 2 years after ablation.
Non-randomized HIFU Clinical Trial

55 Patients with Large HCC (Mean Tumour size: 8.18cm)

- TNM Stage II (15 Patients)
- TNM Stage III (16 Patients)
- TNM Stage IVA (24 Patients)

**Characteristics of the Patients**

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<tr>
<td>Gender (M/F)</td>
<td>43/12</td>
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<tr>
<td>Mean Age (years)</td>
<td>$51.6 \pm 13.05$ (24-73)</td>
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<tr>
<td>Mean Tumor Size(cm)</td>
<td>$8.18 \pm 3.37$ (4-14)</td>
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<tr>
<td>No. of Lesion</td>
<td></td>
</tr>
<tr>
<td>1 lesion</td>
<td>27</td>
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<tr>
<td>2/3/4 lesions</td>
<td>8/9/11</td>
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<tr>
<td>Needle Biopsy (+)</td>
<td>23</td>
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<tr>
<td>AFP(+) plus CT/MRI</td>
<td>32</td>
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<tr>
<td>Hepatitis B/C (+)</td>
<td>48/5</td>
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<td>Child-Pugh class(A/B)</td>
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<tr>
<td>Previous Therapies</td>
<td>22</td>
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<tr>
<td>TNM stages (II/III/IVA)</td>
<td>15/16/24</td>
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Cumulative Survival Curves

Before HIFU                      5 months after HIFU
Contrast-Enhanced MRI, T1WI

Before HIFU                      5 months After HIFU
Contrast-Enhanced MRI, T1WI
Long-term Follow-up Results of Small HCC Patients Treated with HIFU


Clinical Center for Tumor Therapy & Institute of Ultrasonic Engineering in Medicine, Chongqing University of Medical Sciences, China
### Characteristics of the Patients with Small HCC

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<td>54.4 ± 11.3</td>
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<tr>
<td>Mean Tumor Size(cm)</td>
<td>4.3 ± 0.6</td>
</tr>
<tr>
<td>Needle biopsy</td>
<td>14</td>
</tr>
<tr>
<td>AFP(+) plus CT/MRI</td>
<td>13</td>
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<td>Hepatitis B/C(+)</td>
<td>23/2</td>
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<td>Child-Pugh class(A/B)</td>
<td>24/3/0</td>
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<tr>
<td>Previous Treatment</td>
<td>3</td>
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<tr>
<td>TNM stages (II/III/IVB)</td>
<td>24/2/1</td>
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</table>
Kaplan-Meier survival curve in patients with small HCC
Enhanced-CT image (at vein phase) changes of a 49-year-old patient with HCC after HIFU treatment. HCC lesion was 5 cm in diameter.
CONCLUSIONS

◆ HIFU ablation is safe, effective and feasible in the treatment of patients with small and large HCCs.
◆ HIFU can improve the quality of life in patients with advanced-stage HCC, downgrade large HCC for subsequent hepatic resection, and establish the bridge between unresectable HCC and liver transplantation.
HIFU APPLICATIONS IN OTHER KINDS OF SOLID MALIGNANCIES
Enhanced-MRI changes in a 48-year-old patient with pancreatic cancer before and after HIFU ablation

Before HIFU

Enhanced-MRI, T1WI

1 week after HIFU

Enhanced-MRI changes in a 36-year-old patients with breast cancer before and after HIFU ablation

Before HIFU

2 weeks after HIFU

MRI changes in a 37-year-old patient with renal cell cancer before and after HIFU ablation.

ECT changes in a patient with femoral and tibial osteosarcoma before and 2 weeks after one-session HIFU. His tumor was 46 cm in longitudinal extent.

Enhanced-MRI changes in a 68-year-old patient with soft tissue sarcoma before and after HIFU ablation.
Enhanced-MRI changes in a 38-year-old patients with uterine fibroid before and after HIFU
Compared to conventional cancer therapies, HIFU is still in infancy.
HIFU’s future depends on not only HIFU technology, but also a close collaboration between Clinical Doctors, Scientists, and Engineers.

Coagulative Necrosis of “HIFU” in Ox Liver *in vitro*

Ultrasound Imaging of “HIFU”

MR Imaging of “HIFU”