A Mechanistic Pilot Study
Investigating the Enhancement of Drug Delivery to Solid Tumors Utilizing High-Intensity Focused Ultrasound

Jasmine Zia, MD
University of Washington, Hwang Lab
Departments of Bioengineering and Gastroenterology
June 2, 2009
Introduction

• Cancer is the second leading cause of death in the United States, accounting for over 550,000 deaths annually.
# 2009 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>766,130</td>
<td>713,220</td>
</tr>
</tbody>
</table>

- **Prostate** 25%
- **Lung & bronchus** 15%
- **Colon & rectum** 10%
- **Urinary bladder** 7%
- **Melanoma of skin** 5%
- **Non-Hodgkin lymphoma** 5%
- **Kidney & renal pelvis** 5%
- **Leukemia** 3%
- **Oral cavity** 3%
- **Pancreas** 3%
- **All Other Sites** 19%

- **Breast** 27%
- **Lung & bronchus** 14%
- **Colon & rectum** 10%
- **Uterine corpus** 6%
- **Non-Hodgkin lymphoma** 4%
- **Melanoma of skin** 4%
- **Thyroid** 4%
- **Kidney & renal pelvis** 3%
- **Oral cavity** 3%
- **Pancreas** 3%
- **All Other Sites** 22%

---

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2009.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>54</td>
<td>66</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>79</td>
<td>89</td>
</tr>
<tr>
<td>Colon</td>
<td>52</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35</td>
<td>42</td>
<td>51</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Melanoma</td>
<td>82</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>48</td>
<td>53</td>
<td>65</td>
</tr>
<tr>
<td>Ovary</td>
<td>37</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>99</td>
</tr>
<tr>
<td>Rectum</td>
<td>49</td>
<td>57</td>
<td>67</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>74</td>
<td>78</td>
<td>81</td>
</tr>
</tbody>
</table>

*5-year relative survival rates based on follow up of patients through 2005.
Introduction

• Clinical results to date have demonstrated overall disappointing success in effective drug delivery for solid tumor malignancies.
  • Monoclonal antibodies
  • Cytokines
  • Viral and non-viral gene therapy
  • Genetically engineered cells
  • Targeted drug delivery systems
  • Dendritic-cell vaccines
Barriers to Effective Drug Delivery to Solid Tumors

- From injection to tumor death/destruction:

- Unique physiological properties of solid tumors:
  - Anomalous vascularization
  - Decreased blood flow
  - Increased interstitial pressures
Current Solid Tumor Treatment Options
(aside from chemotherapy and radiation...)

• **Open surgery:**
  • Associated with significant morbidity and mortality
  • Suppression of immune system -> increased risk of perioperative metastatic tumor dissemination
  • Post-operative recovery and pain

• **Laparoscopic surgery:**
  • Although quicker recovery time -> still associated with similar risks as open surgery.

• **Minimally invasive techniques:**
  • Radiofrequency ablation, laser ablation, cryoablation, brachy-therapies, thermoablation
    • Risk of bleeding
    • Risk of tumor dissemination
Ideal Localized Solid Tumor Treatment

• Complete death of ALL cancer cells
• No damage to surrounding normal tissues
• No increased risk of tumor cell dissemination
High-Intensity Focused Ultrasound (HIFU)

Highly Focused Transducer Emits An Ultrasound Wave

Focus

Ultrasound Wave Converges to a Focus
High-Intensity Focused Ultrasound (HIFU)

• Definition of Ultrasound:
  • Mechanical vibrations above the threshold of human hearing (16kHz).

• Diagnostic Medical Ultrasound:
  • Frequency: 1 - 20 MHz
  • Intensities: 0.1 - 100 mW/cm²
  • Pressures: 0.001 - 3 MPa

• HIFU:
  • Frequency: 0.8 - 3.5 MHz
  • Intensities: 100 - 10,000 W/cm²
  • Pressures: 10 - 30 MPa
High-Intensity Focused Ultrasound (HIFU)
Mechanisms of HIFU

• **Conversion of mechanical energy to heat**
  • Tissue temperatures rise to 55-80°C in < 1 second -> coagulation necrosis of tumor cells -> irreversible cell death.

• **Inertial cavitation**
  • Alternating cycles of compression and rarefaction
  • During rarefaction, gas drawn out from solution forming bubbles which collapse rapidly -> mechanical stress + thermal insult at microscopic level -> cell necrosis.

• **Anti-tumor host response?**
  • Persistence of tumor antigen in disrupted tumor cells -> host recognition and enhanced T-cell immunity.
High-Intensity Focused Ultrasound (HIFU)

H&E

NADH viability staining
Advantages of HIFU

• **NON-invasive.** Cell death theoretically ONLY at focus of HIFU beam thereby posing NO damage to surrounding tissues, organs and vasculature.

• **NOT tumor specific**

• **NO limit on number of treatments**

• **NO tumor seeding** along needle track

• **NO risk of hemorrhage** from visceral or vascular puncture
Limitations of HIFU

- Requires an **ACOUSTIC WINDOW**
  - No lung or bowel

- **Attenuation**

- **Volume able to treat is 1-3mm x 8-15mm**

- **Unable to obtain tissue for pathology**

- **Skin toxicity** Energy deposition outside the focal region maximal at interfaces between tissues of differing acoustic impedance

- **Pain at site of exposed site**

- **Infection** Abscess formation following bacterial colonization of necrotic volume.

- **Dissemination of tumor cells**
Current Applications of HIFU

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Number of patients</th>
<th>Type of device</th>
<th>Type of study</th>
<th>End points or outcome measures</th>
<th>Outcomes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>20</td>
<td>Transrectal (Sonablate)</td>
<td>Preliminary report</td>
<td>Negative biopsy rate; PSA stability</td>
<td>Complete response in 100% of patients (mean follow-up 13.5 months)</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>402</td>
<td>Transrectal (Ablatherm)</td>
<td>Phase II/III prospective multicentre trial</td>
<td>Safety and efficacy</td>
<td>87.2% negative biopsy rate (mean follow-up 407 days)</td>
<td>4</td>
</tr>
<tr>
<td>Liver</td>
<td>11</td>
<td>Extracorporeal (HAIFU)</td>
<td>Preliminary report</td>
<td>Safety and performance</td>
<td>No major complications; evidence of ablation in 10 of 11 patients (91%)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>474</td>
<td>Extracorporeal (HAIFU)</td>
<td>Case series</td>
<td>No specific criteria quoted</td>
<td>Complete coagulative necrosis seen on histology; absence of contrast uptake in treated region on MRI and subsequent shrinkage over time</td>
<td>6</td>
</tr>
<tr>
<td>Breast</td>
<td>23</td>
<td>Extracorporeal (HAIFU)</td>
<td>Prospective randomized controlled trial</td>
<td>Pathological assessment of therapeutic response</td>
<td>100% response</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Extracorporeal (Exablate)</td>
<td>Feasibility study</td>
<td>Negative biopsy rate</td>
<td>19 of 24 patients (79%) had negative biopsy results after 1 or 2 treatment sessions</td>
<td>7</td>
</tr>
<tr>
<td>Kidney</td>
<td>13</td>
<td>Extracorporeal (HAIFU)</td>
<td>Preliminary report</td>
<td>Symptoms; MRI/CT appearances</td>
<td>Absent contrast uptake on post-HIFU MRI with tumour shrinkage over time; symptom alleviation in most cases; stability of lung metastases</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Extracorporeal (SonoMedical prototype)</td>
<td>Case report</td>
<td>MRI appearance post-treatment</td>
<td>Necrosis and shrinkage over time in 2 of 3 treated tumours</td>
<td>33</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>153 (bone) and 77 (soft tissue)</td>
<td>Extracorporeal (HAIFU)</td>
<td>Case series</td>
<td>Anatomical and functional imaging appearances</td>
<td>Absence of contrast uptake in treated volume on MRI; ablation of tumour on SPECT; destruction of microvasculature on DSA</td>
<td>6</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>55</td>
<td>Extracorporeal (Exablate)</td>
<td>Feasibility study</td>
<td>Safety and feasibility</td>
<td>No major complications; MRI guidance provides safe, accurate delivery of HIFU</td>
<td>27</td>
</tr>
</tbody>
</table>

CT, computed tomography; DSA, digital subtraction angiography; HIFU, high-intensity focused ultrasound; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; SPECT, single-photon-emission computed tomography.

Despite Doubts, Cancer Therapy Draws Patients

By STEPHANIE SAUL
Published: January 18, 2008

PUERTO VALLARTA, Mexico — Some weekends, more than a dozen American men wait at beachfront hotels, anxious for their turns in the treatment room at a small private hospital here.
Current Applications of HIFU

• 1950s: focal neurological treatment (Parkinson’s)
• Ablation of foci of ectopic electrical activity of the heart
• Hemostasis
• Thrombolysis
What about HIFU and Drug Delivery?

• From injection to tumor death/destruction:

Drug injection → Drug localization of tumor site → Solid Tumor → Blood Vessel

Drug molecule
Previous Mechanistic HIFU Studies

• Preliminary mechanistic study by Yuh et al demonstrated increased tumor blood vessel permeability after delivery of HIFU.

• Mice with subQ injections squamous cell carcinoma in flank.

• HIFU delivered to tumor

• Fluorescent nanoparticles, models for drug molecules, were injected into tail vein of mice
Results from Yuh et al Study

CONTROL: 30 pulses

FITC, 30 pulses

CONTROL: 150 pulses

FITC, 150 pulses
Our Hypothesis

High-intensity focused ultrasound will increase drug molecule diffusion in tissue interstitium and thereby enhance solid tumor drug delivery.
Tissue Immersion Assays

Tissue holder #1

Acoustic absorber

Liver specimen

Nanoparticle solution

Tissue holder #2
Tissue Immersion Assays

HIFU

- Custom-built truncated cone attached to transducer, filled with degassed water.
- Aperture diameter of tip of cone: 8mm
- Focus of transducer output manufactured to be at tip of cone
Variables

- **Fluorescent Nanoparticle Size**
  - 20 kDa, 500 kDa

- **HIFU**
  - Frequency: 1 Hz, 4 Hz
  - Length of treatment: 2 min, 10 min

- **Incubation period**
  - 8 min
No Nano/HIFU Controls

2 min 2 min HIFU 8 min incubation 10 min

1 Hz

4 Hz
No HIFU Controls - 20kDa

Approximately 300 - 400 μm of penetration in each case
No HIFU Controls - 500kDa

2 min

10 min

Approximately 50 - 400 μm of penetration
500 kDa

No HIFU

2 min 4Hz

2 min HIFU 4Hz

8 min inc.
500 kDa

No HIFU

10 min 1Hz

10 min 1Hz
damage
Future Directions

• Animal model studies
• Way of marking tissue where HIFU focus point is…
  • Raster spacing?
  • Area of HIFU effects
• Polystyrene fluorescent nanoparticles
• TEM analysis
References

• American Cancer Association website: http://www.cancer.org/docroot/home/index.asp
Acknowledgements

• Principal Investigator:
  • Joo Ha Hwang, MD
  • Yak-nam Wang, PhD
  • Yufeng Zhou, PhD
  • Hong Shen, PhD
• Medicine Residency