Liver Directed Therapy for Hepatocellular Carcinoma

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Combination of 2 diseases

Resection and transplantation offer best chance of cure

≈20% of patients are candidates for surgical intervention

Liver directed therapy offers the mainstay in treatment

Broadly liver directed treatment:

• Ablation
• Transarterial therapy
Ablation

Destruction of the tumor through thermal, chemical or electrical energy
Ablation

- **Thermal**
  - Radiofrequency ablation
  - Microwave ablation
  - Cryoablation

- **Electrical**
  - Irreversible electroporation

- **Chemical**
  - Alcohol
RFA - Physics
RFA: Mechanism of cell death

Caogulative necrosis of tumor by heating the tissue to a $>60°$ C
RFA case

- 62 year old man with cryptogenic cirrhosis
- Screening ultrasound revealed a 2 cm lesion in segment 6
- Child B ECOG 0
- Sedation vs GA
- Temperature 100° for 4-6 mts. Repeat if necessary
- Tract ablation
- Discharged the same day
RFA: Pre and Post

Post ablation 6 month MRI
RFA: Limitations

- RF Electric Current (Intensity)
- Distance between electrode and tissue
- Carbonization (Charring) around electrode tip
- Microbubbles due to vaporization
- Tumor margin
- Target volume with 5-10 mm safety margin

Blood Vessel
RF Electrode
Incomplete ablation
Complete ablation
RFA limitations

- **Tumor size (Ideal ≤ 3cm)**
- **Location:**
  - Adjacent to major blood vessels (Heat sink effect)
  - Inaccessible areas: close to the dome of the liver/caudate
- **Number ≤ 3**
Microwave ablation - Physics

Interaction between water molecules and microwave

Microwave

Water Molecule Orientation
RFA vs Microwave

- Charring does not influence heat dissipation.
- Larger ablations.
- Time required to do the ablation is less.
- Less susceptible to heat sink.

Larger Ablations

- RF: 1.6-2.0 cm diameter
- Microwave: 2.5-3.5 cm diameter

RF vs. MW

Temperature vs. Time graph

17 ga applicators, In vivo kidney
Measured 0.5 cm radially from applicator
Microwave ablation

100 watts for 4 minutes ablation zone 4X3.4cm
Thermal ablation: Complications

- Abscess
- Peritoneal hemorrhage
- Biloma
- Ground pad burn
- Pneumothorax
- Vasovagal reflex
- Biliary tract injury
- Diaphragmatic injury
- Gastric ulcer
- Hemothorax
- Hepatic failure
- Hepatic infarction
- Renal injury
- Sepsis
- Transient ischemic attack
Cryoablation

- Joule-Thompson effect
- Mechanism of action
Lethal temp -20°C to -40°C

Excellent visualization of the ice-ball

Specific risk-bleeding, cryoshock
Mechanism of action

- High voltage direct electrical current.
- Permanent nanopores in the cellular membrane.
- Disrupt the cellular homeostasis, resulting in cell death via apoptosis.
Chemical Ablation

- Intra-tumoral injection of 95% ethanol
- Cells-dehydration and protein denaturation
- Volume calculation: \( V = \frac{4}{3} \pi (r+0.5)^3 \)
<table>
<thead>
<tr>
<th>Study</th>
<th>RFA vs. Surgery</th>
<th>Tumor size</th>
<th>Mortality rate %</th>
<th>Major morbidity rate %</th>
<th>OS %</th>
<th>Disease-free Survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2006</td>
<td>71 vs. 90</td>
<td>Single ≤5cm</td>
<td>0 vs. 1.1</td>
<td>4.2 vs. 55.6</td>
<td>4-yr, 67.9 vs. 64</td>
<td>4-yr, 46.4 vs. 51.6</td>
</tr>
<tr>
<td>Lu 2006</td>
<td>51 vs. 54</td>
<td>Single ≤5 or ≤3 nodules of ≤3cm</td>
<td>0 vs. 0</td>
<td>8 vs. 11</td>
<td>3-yr, 87.1 vs. 86.4</td>
<td>3-yr, 51.3 vs. 82.34</td>
</tr>
<tr>
<td>Feng 2012</td>
<td>84 vs 84</td>
<td>Single or 2 nodules &lt;4cm</td>
<td>0 Vs 0</td>
<td>9.5 vs 21</td>
<td>3-yr, 67 vs 74</td>
<td>3 –yr, 37 vs 49</td>
</tr>
</tbody>
</table>

Randomized Control studies
Only one RCT:

This study was positive for less local recurrence in the Cryo group than in the RFA group.
Complications, Overall survival was higher with MWA, recurrence rates much lower.

<table>
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<th>Mortality rate %</th>
<th>Major morbidity rate %</th>
<th>OS %</th>
<th>Recurrence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelaziz 2014</td>
<td>45 vs 54.</td>
<td>Single ≤5cm</td>
<td>0 vs. 0</td>
<td>11 vs. 3.2</td>
<td>2-yr, 47 vs. 63</td>
<td>13.5 vs. 3.9</td>
</tr>
<tr>
<td>Lu 2005</td>
<td>53 vs.42</td>
<td>Single≤5 or ≤3 nodule of ≤3cm</td>
<td>0 vs. 0</td>
<td>8.2 vs. 5.7</td>
<td>3-yr, 37.6 vs. 50.5</td>
<td>20.9 vs. 11.8</td>
</tr>
</tbody>
</table>
Transarterial therapy

Vascular occlusion through intra-arterially delivered materials
Tumoral Angiogenesis leads to higher MVD in tumors compared to normal liver

Dual blood supply to the liver; Preferential hepatic arterial supply to the tumor
Transarterial therapies

- Hepatic artery embolization with bland particles (TAE)
- Chemoembolization with Lipoidol, chemotherapeutic agents, gelfoam or particles (cTACE)
- Chemoembolization with drug eluting beads (DEB-TACE)
- Y-90 Radioembolization (Y-90)
cTACE

Lipoidol, Doxorubicin, Mitomycin, Cisplatinum, Gel foam or PVA particles
**TACE complications**

- Post Embolization syndrome: 50-60%
- Liver/renal failure: 1-2%
- Abscess: 1-2%
Meta-analysis of RCTs on TACE/TAE

Figure 2. Plot illustrates findings from the meta-regression analysis of an overall 2-year mortality odds ratio and 95% CIs according to different chemoembolization procedures. The bold solid vertical line represents the equivalence line (odds ratio of 1) between treatment and control (C) groups. Odds ratios of less than 1 (to the left of the equivalence line) favor treatment, and odds ratios of greater than 1 (to the right of the equivalence line) favor control group. When the error bar does not cross the equivalence line, a significant difference exists between treatment and control groups. Data are shown on a logarithmic scale. ● = the odds ratio for each comparison. The error bars represent the 95% CIs of each estimate. TAC = transarterial chemotherapy, #Pts = number of patients.
Drug eluting Beads

- Allows sustained release of drug over 2 weeks
- Less post embolization syndrome
- No difference in response rates/Disease control
- Reduction in liver toxicity and Doxorubicin related side effects
## DEB-TACE survival Data

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>PFS</th>
<th>OS from TACE</th>
<th>OS from Diagnosis</th>
<th>1yr, 2yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>130</td>
<td>5.7</td>
<td>14.7</td>
<td>27.6</td>
<td>52%, 32%</td>
</tr>
<tr>
<td>BCLC A</td>
<td>12</td>
<td>10.2</td>
<td>-</td>
<td>-</td>
<td>100%, 75%</td>
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<tr>
<td>BCLC B</td>
<td>33</td>
<td>6.5</td>
<td>15.4</td>
<td>36.6</td>
<td>63%, 31%</td>
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<tr>
<td>BCLC C</td>
<td>81</td>
<td>5.1</td>
<td>13</td>
<td>22.9</td>
<td>47%, 32%</td>
</tr>
<tr>
<td>BCLC D</td>
<td>4</td>
<td>3.7</td>
<td>8.8</td>
<td>23.2</td>
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<tr>
<td>BCLC Stage</td>
<td>Performance Status</td>
<td>Tumor Features</td>
<td>Liver Functions</td>
<td>Treatment options</td>
<td>Survival data</td>
</tr>
<tr>
<td>------------</td>
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<td>----------------</td>
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</tr>
<tr>
<td>0</td>
<td>0</td>
<td>Single &lt; 2cm</td>
<td>No PH, Nor T bili</td>
<td>Surgery or Ablation</td>
<td>OS &gt;60 mo 5yr-75%</td>
</tr>
<tr>
<td>A</td>
<td>0</td>
<td>Single &lt;5cm, Three &lt;3cm</td>
<td>PH, ↑ T bili</td>
<td>Transplant Ablation</td>
<td>OS &gt;60 mo 5yr-75%</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>Multinodular</td>
<td>CP A-B</td>
<td>Transarterial treatments</td>
<td>OS 20 mo SD 14-45 mo</td>
</tr>
<tr>
<td>C</td>
<td>1-2</td>
<td>Vascular invasion, Metastatic</td>
<td>CP A-B</td>
<td>Sorafinib</td>
<td>OS 11 mo SD 6-14 mo</td>
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<tr>
<td>D</td>
<td>3-4</td>
<td>Any</td>
<td>CP C</td>
<td>Supportive care</td>
<td>OS &lt;3 mo</td>
</tr>
</tbody>
</table>
High energy $\beta$ emitter

- Average penetration: 2.5 mm, max 11mm
- Decays to Zincronium 90, $T_1/2 = 64.2$ hrs
- 94% dose delivered at 11 days
Planning Y 90 therapy

CT/MRI imaging review

Planning angiography

Liver to lung shunt estimation

Administration of Y 90

2 weeks

2 weeks
After 3 month of bilateral treatment
Complications Y 90

- Gastrointestinal ulceration: 3-5%
- Radiation Cholecystitis: <1%
- Radiation induced liver disease: <1%
- Radiation pulmonary fibrosis: <1%
- Pancytopenia: <1%
Multi-center Study in Europe

Data from Salem et al

Median OS

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<thead>
<tr>
<th></th>
<th>Radioembolization</th>
<th>Chemoembolization</th>
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<tbody>
<tr>
<td>All</td>
<td>12.8</td>
<td>5.9</td>
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<tr>
<td>BCLC A</td>
<td>26.9</td>
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<td>10.7</td>
</tr>
<tr>
<td>BCLC D</td>
<td>5.3</td>
<td>5.2</td>
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Number at risk

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<th>Chemoem.</th>
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<td>122</td>
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<td>40</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>45</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>0</td>
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Salem Gastroenterology 2011
Multi-disciplinary decision making improves patient outcome

Liver directed therapy is the main stay treatment for HCC

Treatment options: Ablation and Transarterial embolization

Combination therapy

Well tolerated treatments with moderate prolongation of overall survival
Thank you