Local ablation for HCC

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Curative treatments for HCC

• Resection, transplantation, ablation
• 5 y Overall Survival 50 – 75 %

• ~ 20 - 27% of patients candidates for surgical treatments
  – Minus 10% when applying restrictive criteria
  – Plus 10-15% with thermal ablation

• Ablation techniques
  – RFA, MWA, PEI, Cryoablation, AAI, IRE, LITT, HIFU

Bolondi et. al, Semin Liver Dis 2012
Ablation techniques

• **Radiofrequency ablation (RFA)**
  - Resistive tissue heating:
  - Alternating electrical current causes oscillation of H₂O molecules (375 to 500 kHz)
  - Dependent on
    • Electrical conductivity
    • Impedance
  - Temperatures ~ 100°C
  - Monopolar vs. multipolar devices

• **Microwave ablation (MWA)**
  - Dielectric hysteresis:
  - Electromagnetic field causes continuous rotation of H₂O molecules (0.9, 2.45 GHz)
  - Frictional heating of H₂O-rich tissues
  - Homogenous distribution of coagulative necrosis
  - Temperatures ~ 160-180°C in few seconds

• **Irreversible Electroporation (IRE)**
  - High frequency high voltage short electrical pulses
  - Nanopores in cell membrane leading to apoptosis
  - Extracellular matrix spared -> no damage to bile ducts/ blood vessels
  - Minimal heat production
# Ablation Techniques

<table>
<thead>
<tr>
<th>Technology</th>
<th>Potential Advantages</th>
<th>Potential Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>RFA</td>
<td>High rates of local control in tumors 3 cm or smaller</td>
<td>High rates of incomplete ablation in tumors larger than 3 cm</td>
</tr>
<tr>
<td></td>
<td>Established safety profile</td>
<td>Heat sink effect in perivascular tumors</td>
</tr>
<tr>
<td></td>
<td>Known limitations</td>
<td>Potential risk of thermal injury to critical structures</td>
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<tr>
<td></td>
<td>Experience in combination treatments (HCC)</td>
<td>Variability in RFA devices</td>
</tr>
<tr>
<td></td>
<td>Widely available</td>
<td></td>
</tr>
<tr>
<td>MWA</td>
<td>Potential to treat tumors larger than 3 cm more effectively</td>
<td>Limited efficacy data (predictability and reproducibility)</td>
</tr>
<tr>
<td></td>
<td>Less impacted by heat sink effect</td>
<td>Limited safety data</td>
</tr>
<tr>
<td></td>
<td>Ability to activate multiple probes at the same time</td>
<td>Potential risk of thermal injury to critical structures (and vessels?)</td>
</tr>
<tr>
<td></td>
<td>No grounding pads required</td>
<td>Variability in MWA devices</td>
</tr>
<tr>
<td>CRYO</td>
<td>Ability to activate multiple probes at the same time</td>
<td>Insufficient clinical data</td>
</tr>
<tr>
<td></td>
<td>Ability to image the ice-ball formation</td>
<td>Risk of bleeding</td>
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<tr>
<td></td>
<td></td>
<td>Risk of cryoshock</td>
</tr>
<tr>
<td>IRE</td>
<td>Potential to treat tumors located in the vicinity of critical structures</td>
<td>Insufficient clinical data</td>
</tr>
<tr>
<td></td>
<td>Heat sink effect not relevant</td>
<td>Neuromuscular blockage and cardiac gating required</td>
</tr>
</tbody>
</table>

Lencioni R et al, Liver Cancer 2015
Indications – BCLC/ outside BCLC

Hepatocellular carcinoma

**Very early stage (0)**
- Single <2 cm
- Child-Pugh A, PS 0

Potential candidate for liver transplantation

- No
- Yes

- Ablation

**Early stage (A)**
- Single or 3 nodules <3 cm
- Child-Pugh A-B, PS 0

- Single

- Portal pressure, bilirubin
  - Normal
  - Increased
  - Associated diseases

- Resection
- Liver transplantation

**Intermediate stage (B)**
- Large multinodular
- Child-Pugh A-B, PS 0

- Three nodules ≤3 cm

- Ablation

**Advanced stage (C)**
- Portal invasion
- Extrahepatic spread
- Child-Pugh A-B, PS 1-2

- Chemoembolization
- Sorafenib

**Terminal stage (D)**
- Child-Pugh C
- PS 3-4

- Best supportive care

Curative treatments

Palliative treatments

Outcomes of local ablation

- Strongest prognostic variables:
  - Child Pugh Score
  - No & size of tumors (single, <2cm)
  - Initial complete response

- Local recurrence rates 7 – 24%
- Major complications 4%
  ➢ 5y OS 40 – 75 %

- !! 80% of the patients develop recurrent disease -> Long-term survival influenced by multiple different interventions

Lencioni et. Al, Hepatology 2010
Sala et. al. Hepatology 2004
Ablation (RFA) versus resection: controversy

• Most data favouring hepatic resection \(^1,^2\)
  – Higher OS/ RFS/ DFS

• HOWEVER other data shows \(^3,^4\)
  – Resection > RFA regarding local recurrence and DFS
  – No significant differences in 1,3,5 y OS, DFS
  – Some series even for tumors up to 5cm

➢ BUT: lower morbidity/ mortality

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1. The Cochrane Library 2013
Indications beyond BCLC?

1. Intermediate stage B?
   - 5 y OS within Milan: 41–77% vs. outside Milan: 20–75%¹
   - Highly heterogenous population ²
     - Tumor burden/ liver function
     - Disease etiology/ comorbidities
   - Varying benefits from TACE

¹ Tiong L, et al., British Journal of Surgery 2011
² Bolondi et. al., Semin Liv Dis 2012
Indications beyond BCLC?

2. Combination therapies?

- OS/ DFS (TACE & ablation) > monotherapy
- Synergistic effects of both treatments
- No validated inclusion criteria/ optimal treatment schedule

Wang et. al, Korean J Radiol, 2016
3. Bridging/ downstaging?

- EASL: Bridging with ablation (1\textsuperscript{st} choice) or TACE (2\textsuperscript{nd} choice) if waiting times exceed 6 month

- Downstaging of patients initially within Milan versus outside Milan
  - Few data favouring concept
  - EASL: place patient on hold until downstaging is achieved and maintain for 3 month

Lu et. al, Hepatology 2005
Ravaioli et. al, Am J Transplant 2008
Microwave ablation for HCC

• Recent review RFA vs. MWA (3 RCT):
  • Complete response, local recurrence, OS similar
  • Subgroup tumors > 3cm: trend towards MWA > RFA
  • Postintervention. fever: MWA > RFA
  • Local recurrence MWA 14% (n = 480)

Luo et al. W J Surg Oncol, 2017
# IRE for HCC?

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Patients</th>
<th>Tumor</th>
<th>IRE sessions</th>
<th>Tumor size, mm</th>
<th>Voltage, V</th>
<th>Duration, µs</th>
<th>Complete ablation rate</th>
<th>LRFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Thomson et al\cite{35}</td>
<td>25</td>
<td>N/A</td>
<td>63</td>
<td>10–80</td>
<td>1500–3000</td>
<td>70</td>
<td>.83</td>
<td>N/A</td>
</tr>
<tr>
<td>2012</td>
<td>Kingham et al\cite{36}</td>
<td>28</td>
<td>65</td>
<td>31</td>
<td>5–50</td>
<td>1500–3000</td>
<td>70</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2013</td>
<td>Cannon et al\cite{37}</td>
<td>44</td>
<td>44</td>
<td>48</td>
<td>11–110</td>
<td>1500–3000</td>
<td>100</td>
<td>1.00</td>
<td>.97</td>
</tr>
<tr>
<td>2014</td>
<td>Hosein et al\cite{38}</td>
<td>28</td>
<td>58</td>
<td>36</td>
<td>12–70</td>
<td>N/A</td>
<td>N/A</td>
<td>1.00</td>
<td>N/A</td>
</tr>
<tr>
<td>2015</td>
<td>Chong et al\cite{39}</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6–26</td>
<td>1500–3000</td>
<td>90–100</td>
<td>.90</td>
<td>N/A</td>
</tr>
<tr>
<td>2015</td>
<td>Sugimoto et al\cite{40}</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>11–28</td>
<td>1500–1800</td>
<td>70</td>
<td>.83</td>
<td>N/A</td>
</tr>
<tr>
<td>2016</td>
<td>Padia et al\cite{41}</td>
<td>20</td>
<td>N/A</td>
<td>N/A</td>
<td>10–33</td>
<td>1500–3000</td>
<td>20–100</td>
<td>1.00</td>
<td>1 year</td>
</tr>
<tr>
<td>2016</td>
<td>Niessen et al\cite{42}</td>
<td>34</td>
<td>65</td>
<td>N/A</td>
<td>2–71</td>
<td>1500</td>
<td>90</td>
<td>.80</td>
<td>6 months</td>
</tr>
</tbody>
</table>

HCC = hepatocellular carcinoma, IRE = irreversible electroporation, LRFS = local recurrence free survival, N/A = not available.

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**Figure A**

- **CHILDA**
- **CHILDB**
- **CHILDC**

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**Figure B**

- **BCLCA**
- **BCLCO**

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Lyo et. al. Medicine 2017

Niessen et. al. Sci Rep 2017
Image-guidance

• Goal: accurate, complete ablation, 0.5 – 1 cm rim
• Access: open, laparoscopy, percutaneous
• Image-guidance: US, CT, MRI

➢ Stereotactic navigation systems
  – Enhanced localization of intrahepatic lesions
  – Enhanced precision in tumor targeting
    • Targeting trajectories
    • “Vanishing” lesions

Lencioni R et al, Liver Cancer 2015
Tinguely et al. Surg Endosc 2017
Stereotactic image-guided procedures

• Percutaneous navigated ablations Bern 2015 -2016
  – 110 patients, 190 malignant liver tumors (97 MWA, 4 IRE)

• 60 HCC patients
  – Target lateral error: 3.4 +/- 2.0 mm
  – Time for probe placement: 8.8 min
  – Complications: 3 % (Grade I/IIb)
  – LOS 1 day (1 – 13)
  – 6 month follow-up:
    • Local recurrence rate: 15%
      – Not influenced by subcapsular location/ vessel proximity/ BCLC
    • Intrahepatic progression: 43%
  – 8 transplanted (TTT 8.7 month)
Stereotactic IRE for HCC

- Multifocal HCC, cryptogenic origin
- Portal hypertension, G2 Varices
- St.p. 3x MWA
- St.p. angiography (attempt TACE) -> complete stenosis of celiac trunc
- Lesion Seg I
MOSCAT for HCC – Endovascular tumor tracking for combined ablation & TACE

Schwalbe M, Tinguely P et al. MITAT Nov 2017
Tinguely P et al. Under review at PLOS ONE
Conclusion – Local ablation for HCC

• Tissue-sparing, locally destructive treatment
• Low morbidity, satisfying long-term outcome

• Challenges -> aims
  – Widen boundaries ablation/ combination therapies -> widen indications for pot. curative therapy
  – Accuracy of probe positioning to create overlapping ablation zones -> treatment of larger tumors
  – Variable ablation zones according to underling liver parenchyma/ tumor characteristics -> prediction of ablation sizes
  – Early assessment of completeness of ablation -> early re-ablation
  – Validation of advanced technology
Thank you for your attention
IRE for HCC?

C. Niessen, Percutaneous Irreversible Electroporation: Long-term survival analysis of 71 patients with inoperable malignant hepatic tumors. Sci Rep 2017
**Strategy of MI navigated ablations of malignant liver tumors**

- **Indication for local ablation**
  - **Thermal ablation feasible**
    - Yes
    - **Percutaneous approach feasible**
      - Yes
      - No, due to
        - need for diagnostic laparoscopy
        - lesions in proximity of organs
        - multiple lesions (>3-5)
        - simultaneous resection of primary
        - combined resection and ablation
    - No, due to
      - stable, limited disease
      - location next to major portal/ biliary structures
      - adjacent to IVC or venous confluens
      - status post major liver resection

- **Irreversible Electroporation**
- **Laparoscopic approach**
Laparoscopic Navigated MWA 2013 - 2015

• Analysis of 54 patients, 346 tumors
  – Liver-specific complications 5.5%
  – Time for registration/calibration 10min
  – Positive learning curve
  – Local recurrence per lesion at 3 month 9 %
    • Successful re-ablation within 6 month: 75%

➢ Challenges of laparoscopic navigation
  – Limited instrument access
  – Long targeting trajectories
  – Organ deformation

Beyer et al. (2016), Stereotactically-navigated percutaneous Irreversible Electroporation (IRE) compared to conventional IRE: a prospective trial. PeerJ 4:e2277; DOI 10.7717/peerj.2277

Table 3  Time required for sterile patient preparation; placement of IRE electrodes and total intervention. Data are presented as means and standard deviations.

<table>
<thead>
<tr>
<th>Conventional or stereotactic</th>
<th>CIRE (n = 10)</th>
<th>SIRE (n = 10)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile patient preparation duration—min</td>
<td>17.1 ± 2.8</td>
<td>16.1 ± 3.8</td>
<td>t(16.4) = 0.67, p = 0.514</td>
</tr>
<tr>
<td>Electrode placement duration—min</td>
<td>87.0 ± 29.9</td>
<td>26.8 ± 7.7</td>
<td>t(10.2) = 6.2, p &lt; 0.001</td>
</tr>
<tr>
<td>Placement time per electrode—min</td>
<td>18.0 ± 4.2</td>
<td>5.9 ± 2.0</td>
<td>t(13.0) = 8.1, p &lt; 0.001</td>
</tr>
<tr>
<td>Procedure time until start of the ablation—min</td>
<td>104.1 ± 28.2</td>
<td>55.2 ± 9.3</td>
<td>t(10.9) = 5.2, p &lt; 0.001</td>
</tr>
</tbody>
</table>
Curative treatments for HCC

Bolondi et. al., Semin Liv Dis 2012
Resection vs. local ablation

• Hepatic resection is more effective than RFA
  – OS (HR 0.56; 95% CI 0.40 to 0.78)
  – two-year survival (HR 0.38; 95% CI 0.17 to 0.84)
  – event-free survival (HR 0.70; 95% CI 0.54 to 0.91)
  – local progression (HR 0.48; 95% CI 0.28 to 0.82)
  – more complications in resection (OR 8.24; 95% CI 2.12 to 31.95)

• Surgical resection compared to RFA had
  – a higher overall survival
  – a higher recurrence-free survival
  – a higher morbidity (complication rate)
Local ablation

History

available for this purpose, because it is not hemosta-
tic, excepting when the heat of the current
becomes sufficient to char the tissues; whereas the
bipolar, or D'Arsonval current, is distinctively dis-
organizing, causing coagulation necrosis and dessi-
cation of the tissues. In this process, the fluids of
the tissues are cooked, the endothelium of the
blood vessels destroyed by the heat of the process
of boiling and subsequently dried up. This
destruction does not extend very far from the end.
MAVERRIC Trial
**Microwave Ablation VERSUS Resection for Resectable Colorectal liver metastases**

- European multicenter cohort study (Stockholm, Bern, Grøningen)

- Aim: To prove that a strategy of first line local thermal ablation of CRLM is not inferior to liver resection

  - **Primary Outcome:** 3-year Overall Survival
  - **STUDY GROUP:** Percutaneous navigated CT- guided ablation
  - **CONTROL GROUP:** Patients that underwent resection for CRLM

- Propensity score-matched analysis

- Currently: 70 patients included (70%)
Beginning of thermal ablation..

- First reports on coagulative necrosis.. 1981
- First reports on radiofrequency hyperthermia in the liver.. 1983

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**Effect of radiofrequency hyperthermia and chemotherapy on primary and secondary hepatic malignancies when used with metronidazole.**


**Abstract**

Hyperthermia is selectively toxic to neoplastic tissue. Since August 1981, 357 patients with incurable tumors in various body areas have been treated with chemotherapy and radiofrequency hyperthermia (RFHT) with adjuvant metronidazole at this center. Of this group, the cases of 102 patients with hepatic tumors are reported here. Patients received one to ten treatment courses, each course consisting of two to five daily RFHT sessions. Systemic temperature rose 0.6 +/- 0.3 degrees C during treatment, and tumor core temperature (measured by percutaneous transhepatic thermistor) reached 39.5 +/- 1.2 degrees C in 38 monitored patients. Results have been encouraging; in particular, among 15 patients with newly diagnosed colorectal metastases limited to the liver (and as yet untreated for their secondary disease), there has been objective partial tumor regression in 66.7%. Side effects have been few. Skin burns and subcutaneous fat necrosis were seen in 3.9% and 13.7% of patients, respectively. Tumor temperature is difficult to measure reliably and does not correlate with machine power or tumor response. A phase III trial is currently underway to determine the efficacy of RFHT and chemotherapy for patients with hepatic metastases from colorectal adenocarcinoma.
Local ablation

- Local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with BCLC 0-A tumors not suitable for surgery (evidence 2A; recommendation 1B). Other ablative therapies, such as microwave or cryoablation, are still under investigation.
- Radiofrequency ablation is recommended in most instances as the main ablative therapy in tumors less than 5 cm due to a significantly better control of the disease (evidence 1iD; recommendation 1A). Ethanol injection is recommended in cases where radiofrequency ablation is not technically feasible (around 10-15%).
- In tumors <2 cm, BCLC 0, both techniques achieve complete responses in more than 90% of cases with good long-term outcome. Whether they can be considered as competitive alternatives to resection is uncertain (evidence 1iA; recommendation 1C).

**Recommendation**

1. **The AASLD suggests that adults with Child’s A cirrhosis and resectable T1 or T2 HCC undergo resection over radiofrequency ablation.**

   Quality/Certainty of Evidence: Moderate

   Strength of Recommendation: Conditional
Ablation beyond BCLC

<table>
<thead>
<tr>
<th>Median OS</th>
<th>Within BCLC</th>
<th>Outside BCLC</th>
</tr>
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<tbody>
<tr>
<td>1 year</td>
<td>96–100 %</td>
<td>78 – 98 %</td>
</tr>
<tr>
<td>3 year</td>
<td>53–92 %</td>
<td>33–94 %</td>
</tr>
<tr>
<td>5 year</td>
<td>41–77 %</td>
<td>20–75 %</td>
</tr>
</tbody>
</table>

Tiong L, et al., British Journal of Surgery 2011