Discussion for abstract 3570

The tumor vascularity and lipiodol deposition predicts risk of disease progression after TACE in patients with unresectable HCC.

Hai –Liang Li et al.

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Disclosure

- Research fund, material: Lilly, Merck, GSK

- Advisor: Merck, Lilly, Celltrion, Taiho, Quintiles
Aim of the study

• BCLC stage B HCC is treated with TACE.
• Early studies did not support the hypothesis that lipiodol deposition is a predictor of overall survival (OS).
• In this study, the *prognostic value of tumor vascularity and lipiodol deposition* as well as other risk factors on OS and TTP were evaluated in BCLC B and C patients.

• Single institution, retrospective study
• cTACE: standard of care with level 1 evidence
  - TACE + embolization > TACE in OS
  - No other technology of TACE is superior to cTACE

Discordance in data:
  - Difference in patient population
  - Difference in cTACE technology
  - Difference in efficacy evaluation
  - Small number of patients
  - Short follow-up duration
  - Retrospective study
# Baseline characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>Subjects with good blood supply (n=101)</th>
<th>Subjects with poor lipiodol deposition (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>88 (87.13%)</td>
<td>62 (84.93%)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (12.87%)</td>
<td>11 (15.07%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median 57.35±11.71</td>
<td>57.01±12.01</td>
</tr>
<tr>
<td><strong>Tumor size (cm)</strong></td>
<td>8.2±4.63</td>
<td>8.41±5.11</td>
</tr>
<tr>
<td><strong>Number of nodules</strong></td>
<td>3.05±3.66</td>
<td>3±2.75</td>
</tr>
<tr>
<td><strong>Child Pugh score</strong></td>
<td>5.54±0.88</td>
<td>5.44±0.86</td>
</tr>
<tr>
<td><strong>AFP</strong></td>
<td>614.74±561.79</td>
<td>598.82±534.36</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td>0.45±0.5</td>
<td>0.52±0.5</td>
</tr>
<tr>
<td><strong>No. of TACE procedures</strong></td>
<td>2.74±1.19</td>
<td>2.49±0.97</td>
</tr>
<tr>
<td><strong>BCLC stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>63 (62.38%)</td>
<td>40 (54.79%)</td>
</tr>
<tr>
<td>C</td>
<td>38 (37.62%)</td>
<td>33 (45.21%)</td>
</tr>
</tbody>
</table>
Intermediate/advanced HCC

Tumor size (cm)  8.2±4.63 cm  8.41±5.11 cm

- Complete necrosis by size:
  - < 2 cm: 69%
  - 4~5 cm: 68%
  - > 6 cm: 13%

- 2 TACEs for complete necrosis
  - single session: 4.6 ± 1.8 cm
  - subsequent session: 6.3 ± 2.6 cm
  - non-response: 7.4 ± 4.4 cm

> 5 cm: rarely achieved compact lipiodolization
  → combined with RT, RFA
  - 5-7 cm: TACE + RT vs TACE → 2-yr OS: 63% vs 42%

Peng et al. JC0 2013
Multiplicity

Number of nodules 3.05±3.66 3±2.75

Retrospective study (n=490)
  single HCC  33.7%
  multiple HCC  14.6%

Kim et al. AP & T 2012
Inclusion criteria and Exclusion criteria

**Inclusion criteria**

1. Diagnosis of HCC (BCLC stage B or C)
2. Child-Pugh grade A or B
3. ECOG score of 0 or 1
4. Received at least two cycles of TACE

**Exclusion criteria**

1. Previous treatment with microwave ablation, radiofrequency ablation, surgical resection or liver transplantation after TACE
2. Platelet count <50×10^9/L
# Multiple TACEs

## No. of TACE procedures

- 2.74 ± 1.19
- 2.49 ± 0.97

- Georgiades et al. Retrospective study (n=116), at least 2 TACE

<table>
<thead>
<tr>
<th></th>
<th>EASL</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} No responder</td>
<td>45%</td>
<td>50%</td>
</tr>
<tr>
<td>2\textsuperscript{nd} responder</td>
<td>44%</td>
<td>47%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>1-year OS</th>
<th>2-year OS</th>
<th>3-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>66 ± 6</td>
<td>41 ± 6</td>
<td>25 ± 6</td>
</tr>
<tr>
<td>N1</td>
<td>53 ± 7</td>
<td>31 ± 7</td>
<td>19 ± 6</td>
</tr>
</tbody>
</table>

- P value: .16 .28 .49

<table>
<thead>
<tr>
<th>Group</th>
<th>1-year OS</th>
<th>2-year OS</th>
<th>3-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1R2</td>
<td>68 ± 10</td>
<td>50 ± 11</td>
<td>37 ± 11</td>
</tr>
<tr>
<td>N1N2</td>
<td>39 ± 10</td>
<td>14 ± 7</td>
<td>&lt;.005*</td>
</tr>
</tbody>
</table>

- P value: .036 .006 <.005\*
Patients diagnosed with HCC (n=101):
- arterial phase of baseline CT
- Based on tumor vascularity and lipiodol deposition after the first TACE

Follow-up visits were done every 2-3 months

Lost patients during follow-up

Number of HCC patients during study period

Excluded patients by criteria

- good blood supply group (n=101): arterial phase of baseline CT
  - good blood supply + good lipiodol deposition (n=59)
  - good blood supply + poor lipiodol deposition (n=42)
- poor lipiodol deposition group (n=73): CT after treatment
  - good blood supply + poor lipiodol deposition (n=42)
  - poor blood supply + poor lipiodol deposition (n=31)
TACE effect evaluation

- after 24 hours: by non-enhanced multi-slice detect CT (MDCT) homogenous *lipiodol retention*
- after 4 weeks: by contrast enhancement CT non-enhancing area + oil retention area: *necrosis*
  residual tumor *vascularization*

• Pre-treatment: vascularity evaluation
  post-treatment: degree of lipiodol uptake
Angiography:
golden standard for tumor vascularity evaluation

- **Intra-procedure imaging**
  - mesenteric celiac angio: detect branch to extra-hepatic structure
    detect extra-hepatic collaterals
  - 3D angio combined with MDCT

- **Delivery of treatment by continuous visualization**
  - targeting and distribution
  - non-target distribution
    confirm by CT(after 24 hours)
Follow-up TACE (> 4 weeks)

- gelatin sponge: re-cannalisation within 1-2 weeks, absorbed after 1 month

- lipiodol is gradually washed out in neovascularized tumor portion (≈ 4 weeks)

- Resuming of normal attenuation value in surrounding normal tissue: 1 month

- viable tumor re-growth: after 3-4 months
Vascularity evaluation

- **Vascularity evaluation**
  - hypervascularity: enhance than adjacent liver tissue or more than 50% hypervascularity
  - hypovascularity: equal to adjacent liver or less than 50% hypervascularity

- **Response criteria:**
  - decrease to < 25%: successful
  - decrease to > 25%: partial

*Wober et al. Clin Hemorheo Microcirc 2014*
Golden standard: hepatic angiography

- Dynamic MRI: prospective (n=37)  
  Yamashita et al. Acra Radiol 1993
- Power doppler sonography (PDS): prospective (n=43), depth < 7cm  
  Hosoki et al. Acta Radiol 1999
- Dynamic susceptibility contrast enhanced MRI (DSC-MRI): prospective (n=17) 
  heterogenous enhancement  
  Tsui et al. Clinical Imaging 2000
- Multiphase helical CT: prospective (n=72)  
  Ebied et al. Cancer 2002
- Levovist power doppler U/S (Levovist US): prospective (n=46)  
- Contrast enhanced U/S: prospective (n=29)  
- Contrast enhanced U/S (CEUS) with multi-slice detection CT (MDCT) 
  prospective (n=40)  
- First-pass perfusion-weighted MRI (FP-MRI)

**Dynamic CT (MDCT) and MRI: preferred as the golden standard for response evaluation after TACE**
Tumor response evaluation

**EASL**: surface of viable part of tumor
**mRECIST**: arterially enhanced part (devascularization)

Choi, EASL, mRECIST > RECIST 1.1

Ronot et al. The Oncologist, 2014
Tumor necrosis and size change

- reduction of diameter (>30%, PR) or SD with necrosis (>50%)

**Kim et al. Radiol 2010**

- **1997-2009: retrospective study (n=50):**
  
  Response depends on vascularity
  
  - hypervascular tumor: 85% responsive
  - hypovascular tumor: 10% responsive

**Lipiodol uptake: Survival depends on lipiodol uptake**

<table>
<thead>
<tr>
<th></th>
<th>1-yr OS</th>
<th>2-yr OS</th>
<th>5-ys OS</th>
</tr>
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<tbody>
<tr>
<td>compact</td>
<td>92.7%</td>
<td>70.7%</td>
<td>52.4%</td>
</tr>
<tr>
<td>incompact</td>
<td>60.8%</td>
<td>28.0%</td>
<td>16.9%</td>
</tr>
</tbody>
</table>

**Kim et al. AP & T 2012**
Hypervascular

Lipiodol uptake

Vascularity

Log-rank test p-value = 0.027

Log-rank test p-value = 0.709

Log-rank test p-value = 0.864

Log-rank test p-value = 0.997
• Ebied et al: based on both vascularity and responsiveness

<table>
<thead>
<tr>
<th>OS (Mo)</th>
<th>Hypervascular responders ( n = 34 ) (%)</th>
<th>Hypervascular nonresponders ( n = 28 ) (%)</th>
<th>Hypovascular responders ( n = 4 ) (%)</th>
<th>Hypovascular nonresponders ( n = 6 ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>34(100)</td>
<td>25(89)</td>
<td>4(100)</td>
<td>5(83)</td>
</tr>
<tr>
<td>12</td>
<td>28(82)</td>
<td>18(44)</td>
<td>2(50)</td>
<td>0(0)</td>
</tr>
<tr>
<td>18</td>
<td>16(47)</td>
<td>4(14)</td>
<td>2(50)</td>
<td>0(0)</td>
</tr>
<tr>
<td>24</td>
<td>9(27)</td>
<td>3(11)</td>
<td>1(25)</td>
<td>0(0)</td>
</tr>
</tbody>
</table>
• **Different vascularity in HCC:**
  - due to differentiation and size
  - different uptake and deposition of lipiodol
  - collaterals
  - based on necrosis and associated hemorrhage

• **Subsequent treatment**
• **Causes of poor lipiodol**
• **Causes of death**
• **Small number of patients**
• Absence of lipiodol deposition
  - missing feeding vessel
  - extra-hepatic collaterals
    - radioembolization
    - systemic therapy
    - supportive care

• Hypervascular tumor:
  TACE is effective

Hypovascular tumor:
  RFA, ethanol
  → Combination with TACE
Stopping rules (shift to other treatment)

Number of TACE correlated with decreased risk of progression

- Most common causes of stopping sequential TACE:
  - diminished hepatic function reserve
  - marked reduction of general health status

- Stopping rule
  - absence of response in 2 TACE
  - inability to reach all main tumor vessels
  - functional deterioration
    - ECOG ≥ 2,
    - hepatic decompensation (Child-Pough C)
    - LDH > 425 UI/ml
    - AST > 100 UI/ml
    - bilirubin > 2.0 mg/dl
    - tumor volume > 50%
Conclusion

• Combined lipiodol retention and tumor vascularity should be considered as predictors of disease progression after TACE

• Poor lipiodol retention may predict a poor TTP and OS despite the blood supply status.

• **Response predictor**
  - TNM: tumor size $<$ 7.0cm
  - nodules: $<$ 5
  - Child-Pough class
  - tumor vascularity
  - portal vein occlusion
  - initial compact lipiodolization  
    (complete necrosis)
  - aFP
No agreement points on cTACE

• Lipiodol:
  - preparation: 10ml (<15ml per session, water-in-lipid)
  - administration
• Anti-cancer agent: cisplatin = adriamycin/epirubicin
• Embolic material: gelatin sponge particle (100~300 microns)
  - resorvable embolisation is recommended
  - lipiodol + particulates
    main tumor necrosis: 13% → 83%
    satellite necrosis : 6% → 53%
• Intervention technical details and device
• Treatment schedule
• Tumor response criteria
• Combination of treatment
• Subsequent treatment

• Response end-points:
  - imaging response (CT)
  - biologic response (aFP)
  - degree of tumor necrosis
  - patient survival
  - QoL