BCLC sub-staging: feasible or not

Yeon Seok Seo, M.D.
Department of Internal Medicine
Korea University College of Medicine
Seoul, Korea
Contents

• BCLC staging system
• Unmet clinical needs of intermediate HCC
• Treatment options for intermediate HCC
• Substaging of intermediate HCC
• Optimal staging of single large HCC
• Summary
BCLC staging system

- Liver function
- Tumor burden
- Performance status

Prognosis
Treatment option
BCLC staging system

**Terminal stage (D)**
- PST 0, Child-Pugh A
- Single < 2 cm
- Portal pressure/bilirubin: Normal
- Associated diseases: No
- Resection, transplantation
- Curative treatments (30-40%) Median OS >60 months, 5-yr survival 40-7

**Advanced stage (C)**
- PST 0-2, Child-Pugh A-B
- Single or 3 nodules ≤ 3 cm, PST 0
- Portal pressure/bilirubin: Increased
- Associated diseases: Yes
- TACE
- Target 20% OS 20 months

**Intermediate stage (B)**
- PST > 2, Child-Pugh C
- Multinodular, PST 0
- Portal invasion, N1, M1, PST 1-2
- Sorafenib
- Target 40% OS 11 months

**Early stage (A)**
- Very early stage (0)
  - Single
  - Portal pressure/bilirubin: Normal
  - Associated diseases: No
  - Resection, RFA
  - Curative treatments (30-40%) Median OS >60 months, 5-yr survival 40-7

**Very early stage (0)**
- Early stage (A)
  - Single or 3 nodules ≤ 3 cm, PST 0
  - Portal pressure/bilirubin: Increased
  - Associated diseases: Yes
  - Resection, transplantation
  - Curative treatments (30-40%) Median OS >60 months, 5-yr survival 40-7

**Supportive care**
- Target 10% OS <3 months

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• Summary
Unmet clinical needs of intermediate HCC patients

- Heterogeneity of BCLC B
- TACE is not the optimal treatment for many patients with BCLC B HCC
- Resection and transplantation can produce long survival in well-selected patients with intermediate HCC
- Sorafenib has shown to be effective in patients with Child-Pugh class A, both in BCLC B and C HCCs.
- Deviations from current guidelines are very frequent in clinical practice.

*Bolondi L, et al. Semin Liver Dis 2012*
## Heterogeneity of BCLC stage B

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilirubin (mg/dl)</strong></td>
<td>0.9</td>
<td>1.6</td>
<td>2.6</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Albumin (g/dl)</strong></td>
<td>4.8</td>
<td>3.6</td>
<td>3.0</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>No</td>
<td>Mild</td>
<td>Mild</td>
<td>Refractory</td>
</tr>
<tr>
<td><strong>Hepatic encephalopathy</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Child-Pugh class</strong></td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td><strong>Number of tumors</strong></td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Diameter of the 2 largest HCC</strong></td>
<td>35-16 mm</td>
<td>60-45 mm</td>
<td>110 mm</td>
<td>19-18 mm</td>
</tr>
<tr>
<td><strong>Potential treatment</strong></td>
<td>Surgery versus combined TACE + RFA</td>
<td>TACE</td>
<td>TACE (?)</td>
<td>None</td>
</tr>
<tr>
<td><strong>Potential for cure</strong></td>
<td>65%</td>
<td>20%</td>
<td>&lt;5%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Tumor stage: BCLC vs mUICC

- **Single nodule**
  - ~2 cm → BCLC 0, mUICC 1
  - >2 cm → BCLC A, mUICC 2

- **2~3 nodules**
  - ~2 cm → BCLC A, mUICC 2
  - 2~3 cm → BCLC A, mUICC 3
  - >3 cm → BCLC B, mUICC 3

- **>3 nodules**
  - ~2 cm → BCLC B, mUICC 2
  - >2 cm → BCLC B, mUICC 3
UICC stage of BCLC B patients

91% stage 3
6% stage 2
3% stage 4

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Prognosis of BCLC B patients according to the mUICC stage
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TACE for HCC


Sorafenib

Resection

Neither multiple tumors nor portal hypertension are surgical contraindications for HCC

Neither multiple tumors nor portal hypertension are surgical contraindications for HCC.
Neither multiple tumors nor portal hypertension are surgical contraindications for HCC
Resection vs TACE for HCC beyond MC: propensity score analysis

Overall survival

Propensity score analysis

Resection vs. TACE for multiple HCC beyond MC

Overall survival curves for PH or TACE

Log-rank, $\chi^2 = 24.246$, $p < 0.001$

Overall survival curves for pts with 2 tumors after PH or TACE

Log-rank, $\chi^2 = 20.866$, $p < 0.001$

Overall survival curves for pts >2 tumors after PH or TACE

Log-rank, $\chi^2 = 4.591$, $p = 0.032$

Treatment options for BCLC B: Japan

Yamakado K and Kudo M. Oncology 2014;87(suppl 1):78-81
## Treatment options for BCLC B: KASL

<table>
<thead>
<tr>
<th>mUICC stage</th>
<th>Best option</th>
<th>Alternative option</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>LT (within MC) TACE RFA (tumor number ≤3)</td>
<td>Resection PEI (tumor number ≤3)</td>
</tr>
<tr>
<td>III</td>
<td>TACE LT (within MC) RFA (tumor number ≤3 and size ≤3 cm)</td>
<td>Resection</td>
</tr>
<tr>
<td>IVa</td>
<td>Sorafenib</td>
<td>EBRT TACE</td>
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### Treatment & survival according to the BCLC stage

<table>
<thead>
<tr>
<th>BCLC Stage</th>
<th>LT</th>
<th>Resection</th>
<th>RFA</th>
<th>TACE</th>
<th>TARE</th>
<th>BSC</th>
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<tbody>
<tr>
<td>BCLC A</td>
<td>34</td>
<td>17</td>
<td>15</td>
<td>27</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>BCLC B</td>
<td>22</td>
<td>9</td>
<td>4</td>
<td>38</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>BCLC C</td>
<td>12</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>BCLC D</td>
<td>39</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td></td>
<td>55</td>
</tr>
</tbody>
</table>

Treatment & survival according to the BCLC stage

Contents

• BCLC staging system
• Unmet clinical needs of intermediate HCC
• Treatment options for intermediate HCC
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Validation of Bolondi’s proposal

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh score</td>
<td>5-7</td>
<td>5-6</td>
<td>7</td>
<td>8-9</td>
</tr>
<tr>
<td>Beyond MC &amp; within UT-7</td>
<td>IN</td>
<td>OUT</td>
<td>OUT</td>
<td>ANY</td>
</tr>
<tr>
<td>ECOG</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0-1</td>
</tr>
<tr>
<td>PVT</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>First option</td>
<td>TACE</td>
<td>TACE or TARE</td>
<td>-</td>
<td>BSC</td>
</tr>
<tr>
<td>Alternative</td>
<td>LT TACE+RFA</td>
<td>Sorafenib</td>
<td>Research trials TACE Sorafenib</td>
<td>LT</td>
</tr>
</tbody>
</table>

*Bolondi L, et al. Semin Liver Dis 2012*
Up-to-7 criteria

Up-to-7 score

Bolondi’s substaging

• “This review was developed based on a roundtable meeting on the occasion of the International Liver Congress hosted by the European Association for the Study of Liver in April 2012, in Barcelona, Spain.”
Validation of Bolondi’s substaging

Validation of Bolondi’s substaging

Modified Bolondi’s substaging

B1a $\rightarrow$ mB1
B1b, B2a $\rightarrow$ mB2
B2b, B3 $\rightarrow$ mB3
B4 $\rightarrow$ mB4

Validation of Bolondi’s substaging

Bolondi's substage

- B1: 29%
- B2: 50%
- B3: 6%
- B4: 15%

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Validation of modified Bolondi’s substaging

Modified Bolondi's substage

- mB1: 20%
- mB2: 35%
- mB3: 30%
- mB4: 15%

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Staging of single large HCC

BCLC B stage HCC

- Safe and feasible:
  - Resection, resection and RFA or resection by novel technique

- Up-to-7 rule:
  - Transplantation

- Unresectable:
  - TACE, TACE and RFA/PEI or novel embolization technique
  - Sorafenib (if TACE is unsuitable or has failed)

Staging of single large HCC

“Finally, regarding the suggested treatment allocation for patients with BCLC B (intermediate-stage) HCC summarized in Figure 1 of the correspondence by Gao and co-workers,1 the BCLC proposals have always stated that patients with a solitary HCC larger than >5 cm that has expansive growth, and who remain free of symptoms, vascular invasion and tumor dissemination after proper imaging evaluation might benefit from surgical resection; disease in such patients should be classified as BCLC stage A.”

BCLC staging system

HCC

PST 0, Child-Pugh A

Very early stage (0)
Single < 2 cm

Early stage (A)
Single or 3 nodules ≤ 3 cm, PST 0

Intermediate stage
Multinodular, PST 0

Advanced stage (C)
Portal invasion, N1, M1, PST 1-2

Terminal stage (D)
PST > 2, Child-Pugh C

Portal pressure/bilirubin

Increased
Associated diseases

Normal
No
Yes

Resection or transplantation
RFA
TACE
Sorafenib
Supportive care

Curative treatments (30-40%)
Median OS >60 months, 5-yr survival 40-70%
Target 20%
Target 40%
Target 10%

OS 20 months
OS 11 months
OS <3 months

Staging of single large HCC

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
<td>Mean</td>
<td>87.3</td>
<td>75.2</td>
<td>51.8</td>
<td>15.9</td>
<td>18.7</td>
</tr>
<tr>
<td>Median</td>
<td>104.4</td>
<td>75.2</td>
<td>32.3</td>
<td>6.3</td>
<td>4.8</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>87.3</td>
<td>72.4</td>
<td>48.7</td>
<td>15.9</td>
<td>18.7</td>
</tr>
<tr>
<td>Median</td>
<td>104.4</td>
<td>66.7</td>
<td>28.4</td>
<td>6.3</td>
<td>4.8</td>
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</tbody>
</table>
Staging of single large HCC

<table>
<thead>
<tr>
<th>Stage</th>
<th>BCLC 0</th>
<th>BCLC A</th>
<th>SLHCC</th>
<th>BCLC B</th>
<th>BCLC C</th>
<th>BCLC D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>87.3</td>
<td>76.1</td>
<td>55.0</td>
<td>48.7</td>
<td>15.9</td>
<td>18.7</td>
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<tr>
<td>Median</td>
<td>104.4</td>
<td>75.2</td>
<td>41.2</td>
<td>28.4</td>
<td>6.3</td>
<td>4.8</td>
</tr>
</tbody>
</table>
Resection vs TACE for single large HCC: propensity score analysis

Comparison of long-term survival: overall survival analysis of propensity-score-matched patients

Survival benefit of liver resection for HCC patients

Survival benefit of liver resection for HCC patients

Survival benefit of liver resection for HCC patients


<table>
<thead>
<tr>
<th>Variables</th>
<th>Sum of squares</th>
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<tr>
<td>Age</td>
<td>-50</td>
</tr>
<tr>
<td>CRPH</td>
<td>+31</td>
</tr>
<tr>
<td>CHILD B</td>
<td>-279</td>
</tr>
<tr>
<td>PST</td>
<td>-335</td>
</tr>
<tr>
<td>AFP</td>
<td>+113</td>
</tr>
<tr>
<td>Macrovascular invasion</td>
<td>0</td>
</tr>
<tr>
<td>Size</td>
<td>0</td>
</tr>
<tr>
<td>N° nodules</td>
<td>+12</td>
</tr>
<tr>
<td>MELD</td>
<td>-534</td>
</tr>
</tbody>
</table>

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

![Graph D](image4)
TACE + RFA

- Reduction of the cooling effect of hepatic blood flow on thermal coagulation by occlusion of hepatic arterial flow by embolization & reduction of portal venous flow by iodized oil and gelatin sponge particles used in TACE fill the peripheral portal vein around the tumor by going through multiple arterioporal communications → RFA can induce a bigger area of necrosis

- The effect of chemotherapeutic anticancer agents on cancer cells enhances the effect of hyperthermia

- TACE before RFA controls micro-lesions, which contribute to recurrence after treatment

- Disruption of intratumoral septa by TACE facilitates heat distribution within the tumor

TACE+RFA vs RFA in BCLC A (RCT)

# TACE+RFA vs TACE in BCLC B

<table>
<thead>
<tr>
<th></th>
<th>TACE (n=156)</th>
<th>TACE+RFA (n=55)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh grade A/B</td>
<td>136 (87.2%)/20 (12.8%)</td>
<td>48 (87.3%)/7 (12.7%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Single tumor</td>
<td>115 (73.7%)</td>
<td>35 (66.2%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>6.0 (5-8)</td>
<td>5.9 (5-8)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

TACE+RFA
Staging of single large HCC
TACE+RFA

BCLC A & positive profile for resection

Single large HCC & positive profile for resection

BCLC B & positive profile for resection

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Summary

• BCLC B stage contains highly heterogeneous population and substaging for this stage is needed for adequate prognosis prediction and treatment decision.

• Although Bolondi’s substaging system was suggested for this purpose, its efficacy seems to be unsatisfactory.

• If available, more aggressive treatment could be beneficial in patients with BCLC B HCC.

• Staging of single large HCC should be reevaluated.

• More data is required to confirm the optimal treatment option for single large HCC.