Management of Intermediate Stage HCC

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Outline

- What is Intermediate Stage HCC?
- Guideline: TACE for Intermediate Stage HCC
- Clinical Practice is Different
- Intermediate Stage HCC is a Heterogeneous Disease
- What should We Treat after TACE Failure or Refractoriness
- Summary and Conclusion
Proposed AASLD-JNCI modification of BCLC staging: unresectable HCC

HCC

Stage 0
PST 0, Child-Pugh A

Very early stage (0)
Single <2 cm
Carcinoma in situ

Stage A–C
Okuda 1–2, PST 0–2, Child-Pugh A–B

Stage D
Okuda 3, PST >2, Child-Pugh C

Termianl stage (D)

Early stage (A)
Single or 3 nodules <3 cm, PS 0

Intermediate stage (B)
Multimodular PS 0

Advanced stage (C)
Portal invasion, N1, M1, PS 1–2

3 nodules ≤3 cm

No

Yes

Increased

Associated diseases

Resection
Liver transplantation (CLT/LDLT)
PEI/RFA

TACE
Sorafenib

Curative treatments (30%)
5-year survival: 40–70%

Randomised controlled trials (RCTs)
(50%)
3-year survival: 10–40%

Symptomatic (20%)
Survival <3 months

What is Intermediate Stage HCC?
Guideline: TACE for Intermediate Stage HCC
Clinical Practice is Different
Intermediate Stage HCC is a Heterogeneous Disease
What should We Treat after TACE Failure or Refractoriness
Summary and Conclusion
Meta-analysis of randomized controlled trials comparing 2-year survival of TAE/TACE versus best supportive care

<table>
<thead>
<tr>
<th>Author, journal, year</th>
<th>Patients</th>
<th>Random effects model (DerSimonian and Laird)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, Gastroenterology. 1998</td>
<td>63</td>
<td><img src="#" alt="Graph" /></td>
</tr>
<tr>
<td>GETCH, NEJM. 1995</td>
<td>96</td>
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<tr>
<td>Lo, Hepatology. 2002</td>
<td>79</td>
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</tr>
<tr>
<td>Llovet, Lancet. 2002</td>
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<tr>
<td>Overall</td>
<td>503</td>
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</tr>
</tbody>
</table>

Expected median OS vs. BSC: ≈ 20 vs. 16 months
3-year overall survival (OS): 26% – 29%

Heterogeneity p = 0.14
Favors treatment
Favors control

z = −2.3
p = 0.017

TAE = transarterial embolization.

TACE for intermediate HCC

• Significant survival benefits demonstrated in multiple RCTs\textsuperscript{1,2}
  – TACE induces extensive tumour necrosis in more than 50% of patients
  – in responders, survival improvement ranges from 20% to 60% at 2 years

• Currently regarded as the standard of care for patients with localized unresectable intermediate HCC\textsuperscript{2,3}

• Careful patient selection necessary to avoid significant toxicity
  – those with well-preserved liver function and multinodular HCC without vascular invasion or extrahepatic spread are best target

• Not appropriate for patients with tumours that occlude portal venous vessels or are more than minimally metastatic\textsuperscript{3}

EASL-EORTC Guideline

Fig. 4. Representation of EASL-EORTC recommendations for treatment according to levels of evidence (NCI classification [2]) and strength of recommendation (GRADE system). RF, radiofrequency ablation; PEI, percutaneous ethanol injection; OLT, orthotopic liver transplantation; LDLT, living donor liver transplantation.
# Current recommendations for TACE as the standard of care in intermediate HCC

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AASLD</strong>(^1)</td>
<td>1st-line non-curative for non-surgical patients with large/multifocal tumours</td>
<td>EHS, vascular invasion</td>
</tr>
<tr>
<td><strong>EASL–EORTC</strong>(^2)</td>
<td>BCLC-B, multi-nodular asymptomatic tumours, without vascular invasion or EHS</td>
<td>Decompensated cirrhosis, advanced liver dysfunction, MVI or EHS</td>
</tr>
<tr>
<td><strong>ESMO</strong>(^3)</td>
<td>BCLC-B, excellent liver function and multinodular asymptomatic tumours without MVI or EHS</td>
<td>Decompensated cirrhosis, MVI, EHS</td>
</tr>
<tr>
<td><strong>APASL</strong>(^4)</td>
<td>1st first-line treatment for patients with unresectable, large/multifocal HCCs without MVI or EHS</td>
<td>Decompensated cirrhosis, MVI, EHS</td>
</tr>
</tbody>
</table>

AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer; EASL, European Association for the Study of the Liver; EHS, extrahepatic spread; EORTC, European Organisation for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology; APASL, Asian Pacific Association for the study of the Liver, MVI, microvascular invasion, EHS, extrahepatic spread

Outline

● What is Intermediate Stage HCC?
● Guideline: TACE for Intermediate Stage HCC
● How about Real life Clinical Practice?
● Intermediate Stage HCC is a Heterogeneous Disease
● What should We Treat after TACE Failure or Refractoriness
● Summary and Conclusion
Surprisingly, clinical practice is different
Only 10-13% of patients present with BCLC stage B at diagnosis in North America, Europe, and China

<table>
<thead>
<tr>
<th>Variable/group</th>
<th>North America (n = 2262)</th>
<th>Europe (n = 2956)</th>
<th>Asia (n = 3329)</th>
<th>China (n = 8683)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCLC stage, n (%)</td>
<td>n = 1507&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n = 1987&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n = 3023</td>
<td>n = 6480</td>
</tr>
<tr>
<td>0</td>
<td>105 (7)</td>
<td>69 (4)</td>
<td>399 (13)</td>
<td>191 (3)</td>
</tr>
<tr>
<td>A</td>
<td>465 (31)</td>
<td>526 (27)</td>
<td>1289 (43)</td>
<td>1969 (30)</td>
</tr>
<tr>
<td>B</td>
<td>156 (10)</td>
<td>234 (12)</td>
<td>384 (13)</td>
<td>590 (9)</td>
</tr>
<tr>
<td>C</td>
<td>626 (42)</td>
<td>999 (50)</td>
<td>908 (30)</td>
<td>3590 (55)</td>
</tr>
<tr>
<td>D</td>
<td>155 (10)</td>
<td>159 (8)</td>
<td>43 (1)</td>
<td>140 (2)</td>
</tr>
<tr>
<td>Child-Pugh status, n (%)</td>
<td>n = 1944</td>
<td>n = 2225</td>
<td>n = 3144</td>
<td>n = 7841</td>
</tr>
<tr>
<td>A</td>
<td>1411 (73)</td>
<td>1593 (72)</td>
<td>2721 (87)</td>
<td>6804 (87)</td>
</tr>
<tr>
<td>B</td>
<td>428 (22)</td>
<td>559 (25)</td>
<td>390 (12)</td>
<td>956 (12)</td>
</tr>
<tr>
<td>C</td>
<td>105 (5)</td>
<td>73 (3)</td>
<td>33 (1)</td>
<td>81 (1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Statistics based on patients with known values.
<sup>b</sup>Includes patients from Taiwan (n = 1585; 48%), South Korea (n = 1226; 37%), and Japan (n = 518; 16%).
<sup>c</sup>Data missing in >30% of patients.

*Park JW, et al. ASCO 2012 abstract #4033*
BRIDGE Study*: TACE was the most frequently used first recorded HCC treatment in North America, China, and the other Asian countries.

*aIncludes patients from Taiwan (n = 1585; 48%), South Korea (n = 1226; 37%), and Japan (n = 518; 16%).
*bPercentages are based on percentage of population with known values.

*Park JW, et al. ASCO 2012 abstract #4033
BRIDGE Study: First Recorded HCC Treatment by BCLC Status

Patients, %

Transplant  Resection  TACE  PEI/RFA  Other locoregional therapy  Sorafenib  Other systemic therapy  Radiotherapy  Palliative care

<table>
<thead>
<tr>
<th>Status</th>
<th>Number</th>
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<tbody>
<tr>
<td>BCLC-0</td>
<td>602</td>
</tr>
<tr>
<td>BCLC-A</td>
<td>2957</td>
</tr>
<tr>
<td>BCLC-B</td>
<td>942</td>
</tr>
<tr>
<td>BCLC-C</td>
<td>4244</td>
</tr>
<tr>
<td>BCLC-D</td>
<td>300</td>
</tr>
</tbody>
</table>

Percentages are based on percent of population with known values. PEI/RFA, percutaneous ethanol injection/radiofrequency ablation; TACE, transarterial chemoembolization.

*Sherman, et al. ILCA 2012*
TACE also in BCLC C-Patients?

Pinter et al., Radiology 2012; 263: 590

- 228 TACE-patients, Medical University of Vienna
- 144 Sorafenib-Patients, 11 Centers Austria
  - Exclusion: OLT, resection, TACE (Sorafenib-group)
  - BCLC C, retrospective: 34 TACE vs. 63 Sorafenib

Whole Cohort

Survival T vs. S: 9.2 vs. 7.4 months, p=0.377

CP A + MVI, EHS (T 15 vs. S 26 pat.)

Survival T vs. S: 14 vs. 9.7 months, p=0.49
Treatment options in intermediate hepatocellular carcinoma patients.

HCC

- ECOG PS 0, Child-Pugh A
  - Very early stage
    - Single < 2 cm
  - ECOG PS 0-2, Child-Pugh A/B
    - Early stage
      - Single or 3 nodules
    - Intermediate stage
      - Multinodular, ECOG PS 0
        - Transplant/Resection (downstaging)
        - TACE +/- RFA or PEI
        - TACE / TAE
        - TACE + sorafenib (experimental)
        - Sorafenib (for those who fail to respond after repeated TACE)
  - ECOG PS > 2, Child-Pugh C
    - Advanced stage
      - Portal invasion
        - N1, M1, ECOG PS 1–2
        - Sorafenib (for TACE-unsuitable)
    - Terminal stage

Outline

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● Clinical Practice is Different
● Intermediate Stage HCC is a Heterogeneous Disease
● What should We Treat after TACE Failure or Refractoriness
● Summary and Conclusion
### Heterogeneity of Intermediate HCC

<table>
<thead>
<tr>
<th>Number</th>
<th>&lt;3 nodules</th>
<th>Multiple (&lt;4)</th>
<th>Multiple (&gt;4-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 cm</td>
<td>Resection•RFA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple (&lt;4)</td>
<td></td>
</tr>
<tr>
<td>≥3 cm</td>
<td></td>
<td>Multiple (&gt;4-10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Tumor Size
- **≤3 cm**: Nodule size ≤3 cm, treatment options include Resection or RFA.
- **≥3 cm**: Nodule size greater than 3 cm, treatment options are more complex and may involve multiple treatments.
- **Huge (≥7-10 cm)**: Nodule size greater than 7 cm but less than 10 cm, treatment options may include more aggressive therapies.

#### Staging
- **NO**: No evidence of lymph node involvement.
- **MO**: No evidence of distant metastasis.
- **VP0, Vv0**: No extrahepatic involvement.

#### Treatment
- **Resection**: Surgical removal of the tumor.
- **RFA**: Radiofrequency ablation, a minimally invasive procedure.

#### Nodules
- **<3 nodules**: Treatment may include surgical resection or RFA.
- **Multiple (<4)**: Treatment may involve a combination of therapies.
- **Multiple (>4-10)**: Treatment may involve more complex strategies.

#### Size
- **<3 cm**: Treatment generally involves localized therapy.
- **≥3 cm**: Treatment may require multidisciplinary approaches.
- **Huge (≥7-10 cm)**: Treatment may involve advanced therapies.

#### Heterogeneity
- **Heterogeneity of Intermediate HCC**: Refers to the variability in tumor characteristics, impacting treatment decisions.
Patients may vary widely in terms of:

- **Tumor burden**
  - Large unresectable or multinodular HCC

- **Liver function: Child–Pugh A and B**
  - A5–B9
  - Ascites, encephalopathy

Even intermediate HCC itself is a heterogeneous patient population.

**Intermediate HCC**

- Single large nodule (≥5 cm) or multifocal disease
- Preserved liver function (Child–Pugh A or B)
- Asymptomatic (ECOG 0)
- No vascular invasion or extrahepatic spread

HCC, hepatocellular carcinoma
Even intermediate HCC itself is a heterogeneous patient population

Patients may vary widely in terms of:
- Tumour burden
  - Large unresectable or multinodular HCC
- Liver function: Child–Pugh A and B
  - A5–B9
  - Ascites, encephalopathy

Intermediate HCC\(^1,2\)

- Single large nodule (≥5 cm) or multifocal disease
- Preserved liver function (Child–Pugh A or B)
- No vascular invasion or extrahepatic spread
- Asymptomatic (ECOG 0)

- Not all patients with intermediate HCC are suitable for TACE\(^4\)
- Evidence of TACE efficacy in intermediate HCC is limited; most studies carried out in the ‘pre-staging’ era with highly heterogeneous protocols\(^3\)

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization

Not only a patient population, but also TACE procedures are heterogeneous!
Overall survival in selected TACE studies

TACE: long-term survival outcomes are unsatisfactory

- 3-Year overall survival: 26%\(^2\)–29%\(^1\)
- Sustained objective response rate (3–6 months): 35%\(^1\)–39%\(^2\)
- No difference in survival of intention-to-treat population between non-responders and control\(^1\)

Meta-Analysis of TACE for HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, Gastroenterology 1998</td>
<td>63</td>
<td>0.53 [0.32–0.89]</td>
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<tr>
<td>GETCH, NEJM 1995</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Bruix, Hepatology 1998</td>
<td>80</td>
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<tr>
<td>Pelletier, J Hepatol 1998</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Lo, Hepatology 2002</td>
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<td>Overall</td>
<td>503</td>
<td></td>
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</tbody>
</table>

Expected median OS vs. BSC: ≈ 20 vs. 16 months
3-year overall survival (OS): 26% – 29%

Outcome assessed = 2-year survival
- Child-Pugh B <10 % of all patients
- Around 10% had tumor portal vein thrombosis
- In most trials no selective TACE

OR = 0.53 [95% CI, 0.32–0.89] \( P = 0.017 \)

LCSGJ TACE Study

Takayasu K et al. Gastroenterology 2006

TACE for unresectable HCC (n=8510)

HCV 74%  Vp0 88%  Single 44%  <5cm 75%

Survival: overall 1y 82%, 3y 47%, 5y 26%

stage I & damage A 1y 98%, 3y 78%, 5y 52%

MST=34 M
Targeted TACE with a superselective catheterization

HCC, 63F
S7, 1cm,

A7, microcatheter
Lip CT
13mo, no local recurrence
Subsegmental TACE for Multiple HCCs
One week after multiple TACEs

Subsegmental TACE for Multiple HCCs

25 months after TACE
Formula for Successful TACE

Radiological tumor response $\uparrow$ + Preservation of liver function $\uparrow$ = Patient benefit (overall survival) $\uparrow$

TACE, transarterial chemoembolization
So, how should we select patients for TACE?

Who is unsuitable for TACE?
Reported absolute contraindications to TACE

Decompensated cirrhosis (Child-Pugh B ≥8) including:
- Jaundice
- Clinical encephalopathy
- Refractory ascites
- Hepato-renal syndrome

Extensive tumor with massive replacement of both entire lobes

Severely reduced portal vein flow (e.g. non-tumoral portal vein occlusion or hepatofugal blood flow)

Technical contraindications to hepatic intra-arterial treatment (e.g. untreatable arteriovenous fistula)

Renal insufficiency (creatinine ≥2 mg/dL or creatinine clearance <30 mL/min)

Reported relative contraindications to TACE

Tumor size ≥10 cm

Comorbidities involving compromised organ function:
- Active cardiovascular disease
- Active lung disease

Untreated varices at high risk of bleeding

Bile-duct occlusion or incompetent papilla due to stent or surgery
OS in All TACE Patients (n=325)

Yamakado K, et al. on behalf of the Japan TACE Study Group
### Sub-classification of TACE Patients and Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>standardised partial regression coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 4$ tumors $\leq 7$cm (within)</td>
<td>0.618</td>
<td>0.0008</td>
</tr>
<tr>
<td>Child-Pugh grade (A)</td>
<td>0.644</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

Yamakado K, et al. on behalf of the Japan TACE Study Group
Subgrouping of Intermediate stage HCCs

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>CP</th>
<th>4 tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 (n=112)</td>
<td>A</td>
<td>Within (≤4 and ≤7 cm)</td>
</tr>
<tr>
<td>B2 (n=112)</td>
<td>A</td>
<td>Beyond (&gt;4 or &gt;7 cm)</td>
</tr>
<tr>
<td>B3 (n=49)</td>
<td>B</td>
<td>Within (≤4 and ≤7 cm)</td>
</tr>
<tr>
<td>B4 (n=52)</td>
<td>B</td>
<td>Beyond (&gt;4 or &gt;7 cm)</td>
</tr>
</tbody>
</table>
Subgroup CP 4 tumors 7cm

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>CP</th>
<th>4 tumors 7cm</th>
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</thead>
<tbody>
<tr>
<td>B1 (n=112)</td>
<td>A</td>
<td>Within</td>
</tr>
<tr>
<td>B2 (n=112)</td>
<td>A</td>
<td>Beyond</td>
</tr>
<tr>
<td>B3 (n=49)</td>
<td>B</td>
<td>Within</td>
</tr>
<tr>
<td>B4 (n=52)</td>
<td>B</td>
<td>Beyond</td>
</tr>
</tbody>
</table>

Yamakado K, et al. on behalf of the Japan TACE Study Group
Heterogeneity of Patients with Intermediate (BCLC B) Hepatocellular Carcinoma: Proposal for a Subclassification to Facilitate Treatment Decisions

Luigi Bolondi, MD¹  Andrew Burroughs, MBChBHons, FMedSci²  Jean-François Dufour, MD³
Peter R. Galle, MD, PhD⁴  Vincenzo Mazzaferro, MD⁵  Fabio Piscaglia, MD, PhD¹
Jean Luc Raoul, MD, PhD⁶  Bruno Sangro, MD, PhD⁷

Unanswered Questions Relating to Transarterial Chemoembolization

Schedules for Repeat Sessions and Stopping Transarterial Chemoembolization
Key Points of Unmet Clinical Needs of Intermediate Hepatocellular Carcinoma Patients

<table>
<thead>
<tr>
<th>Current Issues with BCLC staging for Intermediate HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The BCLC staging system does not account for the heterogeneity of the intermediate HCC population. This has both prognostic and therapeutic implications and hinders determining the best treatment algorithm. As in the early-stage HCC (BCLC stage A), a subclassification of intermediate HCC based on tumor burden and functional status is required.</td>
</tr>
<tr>
<td>2. ECOG PS is subjective, difficult to define, and does not discriminate between cancer- or cirrhosis-related symptoms.</td>
</tr>
<tr>
<td>3. TACE is the only recommended first-line treatment for intermediate HCC, although it does not seem to benefit all BCLC B patients. As a consequence, various other treatments are employed in the real world on an empirical basis, as first-line therapeutic alternatives for patients unsuitable for TACE or as second-line treatments.</td>
</tr>
<tr>
<td>4. Current recommendations for TACE in intermediate HCC are based on limited data derived from old studies lacking reliable prognostic characteristics and including both early-stage and advanced HCC patients.</td>
</tr>
<tr>
<td>5. TACE is not the optimal treatment for many patients with intermediate HCC. In some subgroups of intermediate HCC patients, there is an increased risk of major complications with TACE, which are further elevated repeated TACE sessions.</td>
</tr>
<tr>
<td>6. Liver resection and transplantation can produce long survival in well-selected patients with intermediate HCC (i.e., limited tumor burden, within the up-to-7 rule or after downstaging). Therefore, this treatment option should be considered for patients who have no extrahepatic contraindications for this procedure.</td>
</tr>
<tr>
<td>7. Sorafenib has shown to be effective and relatively well tolerated in patients with Child–Pugh class A status, both in the intermediate and advanced settings.</td>
</tr>
<tr>
<td>8. Deviations from current guidelines are very frequent in clinical practice. An efficient and evidence-based stratification of intermediate HCC patients may limit arbitrary decisions and make practice more consistent.</td>
</tr>
</tbody>
</table>

HCC, Hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization.

Refinement of BCLC classification

- Subclassification of intermediate HCC (B1–B4) has been proposed based on factors that influence allocation of patients to TACE or alternative treatment:
  - Major and minor tumor burden
  - Liver function by Child–Pugh score and class, presence/absence of jaundice and ascites
  - Presence of PVT
- The proposed subgroups are linked to suggested first-line and alternative treatment options
  - In practice, treatment selection should always be based on careful evaluation of individual patients’ characteristics by a multidisciplinary team

PVT = portal vein thrombosis.

Substaging and treatment indications for patients at first observation with intermediate hepatocellular carcinoma

<table>
<thead>
<tr>
<th>BCLC Sub-Stage</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT score</td>
<td>5-6-7</td>
<td>5-6</td>
<td>7</td>
<td>8-9*</td>
</tr>
<tr>
<td>Beyond Milan and within Ut-7</td>
<td>IN</td>
<td>OUT</td>
<td>OUT</td>
<td>ANY</td>
</tr>
<tr>
<td>ECOG (Tumor Related) PS</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>1st option</td>
<td>TACE</td>
<td>TACE or TARE</td>
<td>BSC</td>
<td></td>
</tr>
<tr>
<td>Alternative</td>
<td>LT</td>
<td>SOR</td>
<td>Research trials TACE SOR</td>
<td>LT**</td>
</tr>
</tbody>
</table>

Bold letters mean stronger scientific evidence.
*, with severe/refractory ascites and/or jaundice;
** only if Up-to-7 IN and PS0;
BSC, best supportive care; LT, liver transplantation; SOR, sorafenib; TARE, transarterial radioembolization

Clinical Validation of a sub-staging proposal of patients with intermediate HCC (BCLC-B)

Results. Survival
VALIDATION OF SUB-STAGING CLASSIFICATION OF PATIENTS WITH INTERMEDIATE HEPATOCELLULAR CARCINOMA (BCLC-B) TREATED WITH CONVENTIONAL TRANSARTERIAL CHEMOEMBOLIZATION

MARCO BIOLATO, ANDREA ZANCHE, VITTORIA VERO, SUMONA RACCO, ELEONORA B. ANNICCHIARICO, MASSIMO SICILIANO, MAURIZIO POMPILI, GIAN LUDOVICO RAPACCINI, ANTONIO GASBARRINI, ANTONIO GRIECO.

Hepatology Unit, Catholic University of Sacred Heart, Rome, Italy
RESULTS

- Mean overall survival of whole population was 31.5 months (95% C.I. 25.9-37.0).

- Number of patients in BCLC subgroup was
  - B1 = 27,
  - B2 = 69,
  - B3 = 15,
  - B4 = 17.

- Each stage appeared associated with different median overall survival (p < 0.05 between groups), namely
  - B1 = 32.0 months (95% C.I. 22.3-41.7)
  - B2 = 21.0 months (95% C.I. 15.5-26.5)
  - B3 = 15.0 months (95% C.I. 10.5-19.5)
  - B4 = 22.0 months (95% C.I. 13.9-30.0)

- The 3-years survival were:
  - B1 = 44.2 %
  - B2 = 22.9 %
  - B3 = 15.2 %
  - B4 = 35.3 % (p<0.05).

Biolato M et al., poster presented at the 64th annual meeting of AASLD (2013)
DISCUSSION / CONCLUSION

• The new substaging proposal is able to refine prognosis of intermediate patients with HCC treated with conventional TACE.

• The prognosis of patients in B2-B3 seems to related mainly on the tumor burden while that of patients in B4 on the underlying cirrhosis, so further studies are needed to confirm the actual prognostic gradient of these substages.

Biolato M et al., poster presented at the 64th annual meeting of AASLD (2013)
Definition of TACE Failure/Refractoriness

- JSH Definition (Kudo M. Dig Dis 2011)
- Park’s Definition (Kim, Park. JGH 2011)
- Raoul’s Definition (Raoul. Cancer Treat Rev. 2011)
- ART Score (Sieghart, Peck. Hepatology 2013)
The ART of Decision Making: Retreatment With Transarterial Chemoembolization in Patients With Hepatocellular Carcinoma

Wolfgang Sieghart, Florian Hucke, Matthias Pinter, Ivo Graziadei, Wolfgang Vogel, Christian Müller, Harald Heinzl, Michael Trauner, and Markus Peck-Radosavljevic

ART-score: Assessment for Retreatment with TACE

The ART score differentiated two groups (0-1.5 points; ≥2.5 points) with distinct prognosis (median OS: 23.7 versus 6.6 months; \( P < 0.001 \)) and a higher ART score was associated with major adverse events after the second TACE (\( P = 0.011 \)). These results were confirmed in the external validation cohort and remained significant irrespective of Child-Pugh stage and the presence of ascites prior the second TACE. Conclusion: An ART score of ≥2.5 prior the second TACE identifies patients with a dismal prognosis who may not profit from further TACE sessions. (Hepatology 2013;57:2261-2273)
The ART-Score to Predict Poor Survival after first TACE
Assessment for Retreatment with TACE: the ART score

• Developed by multivariate regression analysis of
  – baseline characteristics
  – radiological response after 1st TACE (EASL-response criteria)
  – changes of liver function after the 1st TACE
• Determined prior to 2nd TACE in BCLC-A*/B patients, who received ≥ 2x TACE
• Training cohort: n=107 (Vienna), validation cohort: n=115 (Innsbruck)

<table>
<thead>
<tr>
<th>ART score category</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of radiological tumour response</td>
<td>1 (0 if present)</td>
</tr>
<tr>
<td>AST increase &gt;25%</td>
<td>4 (0 if absent)</td>
</tr>
<tr>
<td>Increase in CP score by 1 point</td>
<td>1.5 (0 if absent)</td>
</tr>
<tr>
<td>Increase in CP score by ≥2 points</td>
<td>3 (0 if absent)</td>
</tr>
</tbody>
</table>

*BCLC-A not suitable for liver transplantation/local ablative treatment
AST, aspartate transaminase; BCLC, Barcelona Clinic Liver Cancer; CP, Child–Pugh; EASL, European Association for the Study of the Liver; TACE, transarterial chemoembolization
ART score validation

Training cohort

- ART-Score
  - 0-1.5: (n=60): 23.7 months (CI: 16-32)
  - ≥ 2.5: (n=37): 6.6 months (CI: 5-9)
  - P=0.001

Validation cohort

- ART-Score
  - 0-1.5: (n=74): 28 months (CI: 23-33)
  - ≥ 2.5: (n=37): 8.1 months (CI: 6-11)
  - P=0.001
Proposed ART-Score based Re-treatment Strategy for TACE

ART score assessment
> 14 days < 90 days after TACE-1

<table>
<thead>
<tr>
<th>ART-score</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of radiologic tumor response</td>
<td>1</td>
</tr>
<tr>
<td>AST increase &gt;25%</td>
<td>4</td>
</tr>
<tr>
<td>Child Pugh score increase</td>
<td>1 point</td>
</tr>
<tr>
<td>≥ 2 points</td>
<td>3</td>
</tr>
</tbody>
</table>

0-1.5 points
Consider re-treatment with TACE

≥ 2.5 points
Consider alternative Strategy, e.g. Sorafenib

First TACE

No EHS No PVT
Child-Pugh A or B

* Consider alternative Strategy, e.g. Sorafenib
ART Score does not work for Japanese patients, who had repeated TACE
A Total Numbers of Patients with Repeated TACE (2004.1.1 – 2011.12.31)

<table>
<thead>
<tr>
<th>A total number of TACE</th>
<th>n=779</th>
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</thead>
<tbody>
<tr>
<td>TACE : 2 or more</td>
<td>n=513</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>≤90 days</td>
<td>49</td>
<td>9.6%</td>
</tr>
<tr>
<td>≤120 days</td>
<td>129</td>
<td>25.1%</td>
</tr>
<tr>
<td>≤150 days</td>
<td>173</td>
<td>33.7%</td>
</tr>
<tr>
<td>≤180 days</td>
<td>214</td>
<td>41.7%</td>
</tr>
<tr>
<td>≤210 days</td>
<td>242</td>
<td>47.2%</td>
</tr>
<tr>
<td>≤240 days</td>
<td>266</td>
<td>51.9%</td>
</tr>
<tr>
<td>≤270 days</td>
<td>289</td>
<td>56.3%</td>
</tr>
<tr>
<td>≤300 days</td>
<td>306</td>
<td>59.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ART score</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>5.5</td>
<td>1</td>
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<tr>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
</tr>
</tbody>
</table>
Overall Survival According to ART Score

<1.5  median 22.4 months (95% CI 13.1 – 31.7)
2.5-8  median 16.5 months (95% CI 0 – 44.3)

P=0.622

Limitation of ART Score as a Measure of TACE Refractoriness

- ART score can be applied only in < 10% of patients with repeated TACE in validation study.
- ART score did not have any impact on survival in patients with 2\textsuperscript{nd} TACE within 90 days.
- ART score is not useful as a measure of TACE refractoriness since it is only applied to the patients who received 2\textsuperscript{nd} TACE within 90 days.
- ART score is not universally applicable point system and not the definition of actual TACE refractoriness after several repeated TACE procedure.
Summary and Conclusion

- TACE is basically recommended for Intermediate stage HCC according to Guideline.
- However, since intermediate stage HCC is a heterogeneous patient population, several treatment options are applied in the real world clinical setting.
- Sub-staging of intermediate stage HCC is an urgent clinical needs.
- Definition of TACE failure/refractoriness is also an important issue in intermediate stage HCC, but has not yet been established.
Emerging Approach to HCC

4th International Kyoto Liver Cancer Symposium

In Conjunction with 50th Anniversary Meeting of Liver Cancer Study Group of Japan

7(Sat.)–8(Sun.) June, 2014
Kyoto International Conference Center, Japan

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e-Posters
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