The Clinical Guidelines Evolution in HCC from BCLC to HKLC - Where Does cTACE Fit In?

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Challenges in Management of HCC

One patient with two diseases

- A highly malignant tumor
  - High propensity for venous invasion
  - Rapid growth (tumor volume doubling time 3 months)
- Associated cirrhosis (80%)
  - Impaired liver function
- Multicentric hepatocarcinogenesis
Current Treatments for HCC

- Liver resection (~20%)
- Liver transplantation (<5%)
- Local ablative therapies (~20%)
- Transarterial chemoembolization / radioembolization (~20%)
- Systemic therapy / supportive care (35%)
Value of cTACE in HCC treatment

- Standard of care procedure for multinodular primary liver cancer (stage B)

- cTACE = Lipiodol® TACE using various cytotoxic drugs

- Used over 3 decades; now benefits to more than 600,000 patients yearly

- More than 100 major clinical studies have been published on cTACE, involving more than 10,000 patients

- Provides 4 additional survival months in stage B HCC patients

(*) http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
# 2 Pivotal RCTs & 1 meta-analysis

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<tbody>
<tr>
<td>cTACE</td>
<td>Symptomatic TT</td>
<td>Doxorubicin</td>
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<td>cTACE</td>
<td>Symptomatic TT</td>
<td>Cisplatin</td>
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Lo C.M. et al. (2002)

- Single center, open-label, randomized, controlled clinical trial
- 79 Asian patients with unresectable HCC (Okuda I/II stage)
  - Chemoembolization group (cTACE with Lipiodol® + cisplatin repeated every 2-3 months): 40 patients
  - Control group (symptomatic treatment): 39 patients
- 1\textsuperscript{ary} endpoint = survival

**Objective:** «... assessed the efficacy of transarterial Lipiodol (Lipiodol® Ultrafluide, Laboratoire Guerbet, Aulnay-Sous-Bois, France) chemoembolization in patients with unresectable hepatocellular carcinoma. »

**Results:** «... transarterial Lipiodol\textsuperscript{®} chemoembolization [...] prolongs the survival of a selected group of Asian patients with unresectable hepatocellular carcinoma and is an effective palliative treatment option. »

<table>
<thead>
<tr>
<th>Probability of survival</th>
<th>cTACE (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>57</td>
<td>32</td>
</tr>
<tr>
<td>2 years</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>3 years</td>
<td>26</td>
<td>3</td>
</tr>
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P = 0.002

Fig. 2. Probability of survival in patients treated with chemoembolization and in patients of the control group (log-rank test, P = .002).
**Systematic review of RCTs** identifying survival benefits of medical interventions (arterial embolization/chemoembolization) for unresectable HCC in comparison with conservative management or suboptimal therapies

**Meta-analysis of 7 RCTs:** 6 studies reporting 2-year death rates (503 patients) + 1 study reporting 1 year survival* (42 patients)

<table>
<thead>
<tr>
<th></th>
<th>TAE / TACE group</th>
<th>Control group</th>
<th>Nb. patients</th>
<th>2-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al.</td>
<td>Particles or gelatin</td>
<td>5-FU</td>
<td>63</td>
<td>20 (TAE) 13 (Ctrl)</td>
</tr>
<tr>
<td>(Gastroenterology 1998)</td>
<td>Particles or gelatin + 5-FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelletier et al.*</td>
<td>Doxorubicin + gelatin</td>
<td>Conservative management</td>
<td>42</td>
<td>24 (TACE) 33 (Ctrl)</td>
</tr>
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<td>(J. Hepatol. 1990)</td>
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</tr>
<tr>
<td>Groupe Etude &amp; Traitement du CHC (NEJM 1995)</td>
<td>Lipiodol® + cisplatin + gelatin</td>
<td>Conservative management</td>
<td>96</td>
<td>38 (cTACE) 26 (Ctrl)</td>
</tr>
<tr>
<td>Bruix et al.</td>
<td>Radiological contrast medium + gelatin</td>
<td>Conservative management</td>
<td>80</td>
<td>49 (TAE) 50 (Ctrl)</td>
</tr>
<tr>
<td>(Hepatology 1998)</td>
<td></td>
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</tr>
<tr>
<td>Pelletier et al.</td>
<td>Lipiodol® + cisplatin + lecithin + gelatin + tamoxifen</td>
<td>Tamoxifen</td>
<td>73</td>
<td>24 (cTACE) 26 (Ctrl)</td>
</tr>
<tr>
<td>(J. Hepatol. 1998)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Lo et al.</td>
<td>Lipiodol® + cisplatin + gelatin</td>
<td>Conservative management</td>
<td>79</td>
<td>31 (cTACE) 11 (Ctrl)</td>
</tr>
<tr>
<td>(Hepatology 2002)</td>
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<tr>
<td>Llovet et al.</td>
<td>Gelatin + Lipiodol® + doxorubicin + gelatin</td>
<td>Conservative management</td>
<td>112</td>
<td>50 (TAE) 63 (cTACE)</td>
</tr>
<tr>
<td>(The Lancet 2002)</td>
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<td>27 (Ctrl)</td>
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</tbody>
</table>

*Hepatology 2003; 37: 429-442
European guidelines

- Recommendations on chemoembolization and transcatheter therapies
  - « Chemoembolization (Lipiodol®) is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra hepatic spread (evidence 1iiA; recommendation 1A) »
  - « The use of drug-eluting beads has shown similar response rates than Gelfoam-Lipiodol® particles associated with less systemic adverse events… »
American, Japanese & Chinese guideline recommendations

- **American guidelines**
  
  « **TACE is recommended as first line non-curative therapy** for non-surgical patients with large / multifocal HCC who do not have vascular invasion or extra hepatic spread (level I) »

  « Chemotherapy has to be injected prior to arterial obstruction. It is usual to suspend chemotherapy in **Lipiodol**®, an oily contrast agent used for lymphographic studies. **Lipiodol**® is selectively retained within the tumor and this expands the exposure of the neoplastic cells to chemotherapy... »

- **Japanese guidelines**
  
  « **Transcatheter arterial chemoembolization/TAE is recommended as treatment for advanced hepatocellular carcinoma** with liver damage stages A and B (inoperable and not candidates for local ablation therapy)... (grade A) »

  « **Lipiodol**®-TACE taking account of hepatic functional reserve and the area of non-cancerous liver tissues to be chemoembolized is recommended for current TACE (grade B). [...] The prognosis of advanced hepatocellular carcinoma or small hepatocellular carcinoma patients with good liver function is favorable after Lip-TACE... »

- **Chinese guidelines**
  
  « **Superselective catheterization is preferred whenever possible, in combination with proper embolization agents. An emulsion mixture of super-liquid Lipiodol**® and chemotherapeutic agents is commonly used for this therapy. **The dosage of iodized oil should depend on the size, blood supply, and feeding arteries of the tumor. »

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(13) Japan Society of Hepatology, Recommendation, Chapter 5, Hepatology Research 2010; 40 (Suppl.1) 96-112
cTACE consensus guidelines endorsement

- TACE = cTACE = Lipiodol® TACE
- Lipiodol® endorsed by
  - European guidelines
  - American guidelines
  - Japanese guidelines
  - Chinese guidelines
HCC classification
Barcelona-Clinic Liver Cancer (BCLC) staging system and treatment strategy

- Stage 0
  - PST 0, Child-Pugh A
  - Very early stage (0)
    - Single <2 cm, Carcinoma in situ
    - Portal pressure/bilirubin
      - Increased
        - Normal
          - Resection
          - Liver transplantation (CLT/LDLT)
        - No
          - RF/PEI
        - Yes
          - TACE
          - Curative treatment (30-40%)
            - Median OS >60 mo; 5-yr survival: 40-70%
          - Target: 20%
            - OS: 20 mo (45-14)

- Stage A-C
  - PST 0-2, Child-Pugh A-B
  - Early stage (A)
    - Single or 3 nodules ≤3 cm, PS 0
    - Associated diseases
      - No
        - Resection
        - Liver transplantation (CLT/LDLT)
        - RF/PEI
        - TACE
        - Curative treatment (30-40%)
          - Median OS >60 mo; 5-yr survival: 40-70%
        - Target: 20%
          - OS: 20 mo (45-14)
      - Yes
        - TACE
        - Target: 20%
          - OS: 11 mo (6-14)

- Stage D
  - PST >2, Child-Pugh C*
  - Advanced stage (C)
    - Portal invasion, N1, M1, PS 1-2
    - Sorafenib
    - Target: 40%
      - OS: 11 mo (6-14)

- Terminal stage (D)
  - Best supportive care
  - Target: 10%
    - OS: <3 mo

References:

PST (Performance Status Test) = PS (Physical Status)
HCC Staging Is Multifaceted

• Staging is used for prognosis and to guide treatment

• Staging HCC
  – Most patients have underlying liver disease
  – Key prognostic indicators are not clearly defined
  – Prognostic indicators vary during the course of disease

• Factors affecting staging systems
  – Tumor stage
  – Liver function
  – Health status
  – Efficacy of treatment

Introduction

• The BCLC staging classification was developed in 1999 based on cohorts of patients in Europe, predominantly HCV-infected.

• It has been endorsed both by the EASL and the AASLD. The latest update was in 2010.

• To date, the BCLC staging classification for HCC is the most popular treatment algorithm in Western countries, but has not commonly used in Asia.

• In Western countries, hepatitis C virus (HCV) infection is the main attributable factor, as well as alcohol-related cirrhosis and possibly nonalcoholic fatty liver disease.
Introduction

- In contrast, in most Asia countries and Africa, the high incidence of HCC is associated with endemic hepatitis B virus (HBV) infection.

- More aggressive treatment approach, especially surgical resection, is adopted in most Asian centers due to higher case volume and expertise.

- An appropriate staging system for HCC with treatment guidelines applicable to Asian patients is urgently needed.
BCLC is Too Conservative in Treatment Recommendation

Many clinicians especially in the East consider that:

• Role of surgical resection can be extended to intermediate or locally advanced HCC with intrahepatic venous invasion

• Role of ablation can be extended to tumor 3-5 cm, or even slightly > 5 cm

• Role of transarterial therapy can be extended to locally advanced HCC with intrahepatic venous invasion
Objective

• To develop a new prognostic classification with treatment recommendations applicable to Asian patients with HCC

• To compare it with the BCLC staging classification
Hong Kong Liver Cancer Staging System with Treatment Stratification for Patients with Hepatocellular Carcinoma

Thomas Yau, Vikki Y.F. Tang, Tzy-Jyun Yao, Sheung-Tat Fan, Chung-Mau Lo, Ronnie T.P. Poon

Gastroenterology 2014 Feb 25.
Staging Systems for Hepatocellular Carcinoma
See Article 1691 and Editorial 1599

1659 Sodium Channel Mutation in Patients With IBS
1680 Risk of β Blockers in Patients With Cirrhosis and SBP
1714 Long Intervening Noncoding RNA POU3F3 in Esophageal Cancer
1763 Effect of Lactate in Experimental Hepatitis and Pancreatitis

ALSO:
• Reviews: Gut Tissue Engineering 1614 & Disorders of Bilirubin Metabolism 1625
• 2014 Julius M. Friedenwald Medal Awardee—Nicholas F. LaRusso, MD 1813
Hong Kong Liver Cancer Staging System with Treatment Stratification for HCC

Prospectively collected data (2026 variables covering demographic, clinical, laboratory, treatment, and survival data) from 3856 patients with HCC (predominantly HBV-related) treated at Queen Mary Hospital from 1995-2008.

Cox regression was used to account for the relative effects of factors in predicting overall survival times.

Classification and regression tree (CART) analyses were used to classify disparate treatment decision rules.

All patients were allocated randomly into a training set or a test set in 1:1 ratio.

Yau et al. Gastroenterology 2014
Results

- 3856 eligible adult HCC patients were included.

- Predominantly hepatitis B carriers (79.90%).

- Four established factors which have determinative roles in treatment were chosen:
  - Physical condition: ECOG performance status (ECOG PS)
  - Liver function: Child-Pugh grade
  - Tumor burden: tumor status, presence of extrahepatic vascular invasion and/or metastasis (EVM)

- 73% of patients had underlying Child-Pugh class A liver function, 21% had class B liver function, and only 6% had class C liver function.
## Results

<table>
<thead>
<tr>
<th>Treatment Modality: First treatment given</th>
<th>Training Set</th>
<th>Test Set</th>
</tr>
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<tbody>
<tr>
<td>Resection</td>
<td>550 (27.95%)</td>
<td>495 (26.22%)</td>
</tr>
<tr>
<td>LT</td>
<td>69 (3.51%)</td>
<td>54 (2.86%)</td>
</tr>
<tr>
<td>Ablation</td>
<td>165 (8.38%)</td>
<td>156 (8.26%)</td>
</tr>
<tr>
<td>TACE</td>
<td>480 (24.39%)</td>
<td>485 (25.69%)</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>321 (16.31%)</td>
<td>325 (17.21%)</td>
</tr>
<tr>
<td>Supportive care</td>
<td>383 (19.46%)</td>
<td>373 (19.76%)</td>
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</tbody>
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**Hong Kong Liver Cancer Staging System**

- Tumors in the liver classified into early, intermediate and advanced based on 0, 1 or \(\geq 2\) adverse prognostic factors:

<table>
<thead>
<tr>
<th>Liver tumor status</th>
<th>Size</th>
<th>Number of nodules</th>
<th>Intrahepatic Venous Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>(\leq 5) cm</td>
<td>(\leq 3)</td>
<td>No</td>
</tr>
<tr>
<td>Intermediate</td>
<td>(\leq 5) cm</td>
<td>(\leq 3)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(\leq 5) cm</td>
<td>(&gt; 3)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(&gt; 5) cm</td>
<td>(\leq 3)</td>
<td>No</td>
</tr>
<tr>
<td>Locally-advanced</td>
<td>(\leq 5) cm</td>
<td>(&gt; 3)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(&gt; 5) cm</td>
<td>(\leq 3)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(&gt; 5) cm</td>
<td>(&gt; 3)</td>
<td>Any</td>
</tr>
<tr>
<td>Diffuse</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>
Hong Kong Liver Cancer Staging System

ECOG 0-1
Child A/B

No EVM*

Early tumor

Stage 1

Resection/LT/ablation

Intermediate tumor

Stage 2

Resection

Locally advanced tumor

Stage 3

Resection/TACE

Systemic therapy

Stage 4

ECOG 2-4
Child C

Early tumor

Stage 5a

Liver Transplantation

Intermediate/advanced tumors

Stage 5b

Supportive care

*EVM, extrahepatic vascular invasion/metastasis
Kaplan-Meier estimated overall survival curves of HKLC staging system
Hypothetical Kaplan-Meier estimated overall survival curves of HKLC scheme and BCLC scheme

Median OS: 16.6 months vs 8.9 months
Survival comparison between patients receiving different treatments according to BCLC scheme (BCLC-B) and HKLC scheme (HKLC-II)

5-year survival probability: 52.1% vs 18.7%; P<0.0001
Survival comparison between patients receiving different treatments according to BCLC scheme (BCLC-C) and HKLC scheme (HKLC-II)

5-year survival probability: 48.6% vs 0%; P<0.0001
Survival comparison between patients receiving different treatments according to BCLC scheme (BCLC-C) and HKLC scheme (HKLC-III).

3-year survival probability: 9.7% vs 1.7%; P<0.001
Key Differences between HKLC and BCLC - Staging Classification

HKLC Staging:

- **Combine ECOG 0 and 1** into one category to reflect clinical practice – patients with symptoms should not be excluded from radical treatment.

- Refined stratification of local tumor(s) in the liver using the triad of **tumor size** (5 cm as cut-off diameter), **tumor number**, and **macroscopic vascular invasion**.

- Separate classification **of locally advanced tumor (stage 3b)** and **tumor with extehepatic venous invasion or metastasis (stage 4)**.

- Unique stage **Va** for **transplantable early HCC associated with Child C cirrhosis** and ECOG >1.
Key Differences between HKLC and BCLC - Treatment Recommendation

- Multifocal tumors or intrahepatic vascular invasion NOT considered contraindication for surgical resection
- Ablation recommended for tumor up to 5 cm
- Intrahepatic vascular invasion NOT considered contraindication for transarterial therapies

More aggressive treatments give better survival outcomes, provided with careful patient selection in terms of liver function reserve
HCC classification
Barcelona-Clinic Liver Cancer (BCLC) staging system and treatment strategy

HCC

Stage 0
PST 0, Child-Pugh A

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

Single
Portal pressure/bilirubin

Increased
Normal

Resection
Liver transplantation (CLT/LDLT)

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

3 nodules ≤3 cm

Associated diseases

No
Yes

RF/PEI

Curative treatment (30-40%)
Median OS >60 mo; 5-yr survival: 40-70%

Intermediate stage (B)
Multinodular, PS 0

Target: 20%
OS: 20 mo (45-14)

TACE

Target: 40%
OS: 11 mo (6-14)

Stage A-C
PST 0-2, Child-Pugh A-B

Stage D
PST >2, Child-Pugh C*

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

Terminal stage (D)

Best supportive care

Sorafenib

cTACE - Standard of care treatment for BCLC intermediate stage HCC patients


PST (Performance Status Test) = PS (Physical Status)
Hong-Kong Liver Cancer Staging System

Expanding use of TACE in HCC patient management

(Yau T. et al., Gastroenterology 2014; 146: 1691-1700)
Validation of HKLC vs. BCLC – Western Study

- A total of 890 American HCC patients between 2000 and 2013 treated by TACE at John Hopkins University (48% HCV, 28.5% alcoholic, 14.8% HBV)

- Both HKLC and BCLC classified survival with high significance (p<0.001)

- HKLC performed better than BCLC across all statistical measures to compare the two systems:
  - Greater homogeneity (p<0.001)
  - Better survival discrimination (C = 0.712 vs. 0.64)
  - Better gradient monotonicity (P<0.001)

Conclusion: HKLC outperformed BCLC as a prognostic classification across all statistical measures in a western HCC patient cohort with HCV as the main etiology

Sohn et al. World Conference of Interventional Oncology 2015
Thank You