Optimal management of HCC: in Asia

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Newly diagnosed HCC: > 70% occur in Asia, > 75% of them are infected with HBV

Regional mortality rates of HCC (per 100,000 persons) categorized by age-adjusted mortality rates

Annual mortality per region:
Europe: 54,000
USA: 19,000
China–Korea–Japan: 390,000

55% of HCC Worldwide
Challenge: surveillance & Dx

Screening and surveillance program are not implemented successfully in many Asian countries.

The majority of HCC patients in Asia still presents with intermediate and advanced stage HCC at diagnosis.
Prevention of hepatocellular carcinoma in the Asia–Pacific region: Consensus statements
Asia–Pacific Working Party on Prevention of Hepatocellular Carcinoma

Table 5  Working Party recommendations 11–14

**Recommendation 11:** Hepatocellular carcinoma (HCC) surveillance is a measure that can reduce mortality from HCC in subgroups of patients with cirrhosis, but is best conducted within an well-organized screening program (level III).

**Recommendation 12:** The recommended surveillance program outside of Japan is liver ultrasound conducted by an experienced centre every 6 months and serum α-fetoprotein performed simultaneously (level III).

**Recommendation 13:** All patients with cirrhosis are recommended for HCC surveillance, unless comorbidity, logistics and patient choice render curative therapy inappropriate (level Iia).

**Recommendation 14:** HCC screening is also recommended for high-risk patients with chronic hepatitis B (especially those aged >30 years with serum hepatitis B virus DNA levels >20 000 IU/mL) in the absence of a known diagnosis of cirrhosis (level III).
# HCC surveillance: Recommendations in different Asian countries

<table>
<thead>
<tr>
<th>Korea</th>
<th>Japan</th>
<th>Taiwan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interval</strong></td>
<td>6 mo</td>
<td>Cirrhosis: 3 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV/HCV carrier: 6 mo</td>
</tr>
<tr>
<td><strong>Test</strong></td>
<td>US+AFP</td>
<td>Cirrhosis: US+AFP+DCP+AFP-L3, every 3-4 mo (dynamic CT/MR, every 6-12 mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV/HCV carrier: US+AFP+DCP+AFP-L3, every 6 mo</td>
</tr>
</tbody>
</table>
Applicability of BCLC stage for prognostic stratification in comparison with other staging systems: single centre experience from long-term clinical outcomes of 1717 treatment-naïve patients with hepatocellular carcinoma

Beom Kyung Kim, Seung Up Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Mi Sung Park, Eun Hye Kim, Jinsil Seong, Do Youn Lee and Kwang-Hyub Han

BCLC

Fig. 1. Cumulative overall survival according to BCLC stage (from stage 0 to stage D).
Optimal managements of HCC in Asia
1. Know enemy (知彼);
2. Know myself (知己);
3. Establish good strategy (必勝戰略, roadmap)
Know enemy (知彼);

- Tumor neovasculature and frequent vascular invasion with intra-and extra-hepatic metastasis
- Great heterogeneity with respect to tumor behavior
- Frequent association with different status of the underlying liver cirrhosis and viral hepatitis
Treatment Options for HCC

- Radical therapies (40%)
  - Surgical resection
  - Liver Transplantation (CLT/LDLT)
  - Local ablation therapy

- Palliative therapies (40-50%)
  - Transarterial embolization/ Chemoembolization
  - Molecular target therapy (sorafenib)
  - Hormonal treatments/ Immunotherapy
  - Antiproliferative agents
  - HAIC
  - Others; pilot therapy; Radiotherapy; external, internal RT, etc
  - Combination therapy

- Symptomatic treatment (10-20%)
Staging Systems of HCC

- To predict the prognosis
- To stratify the patients according to prognostic variables in the setting of clinical trials
- To guide therapeutic approach
AASLD Practice Guideline: BCLC Staging and Treatment Strategy

Lovett et al, 2008

50%-70% 5 years

10%-40% 3 years

(30-40%)

(20%)

(40%)

(10%)

Lovett et al, 2008
APASL Guidelines

HCC

Confined to the liver
Main portal vein patent
Resectable

Yes
Resection/RFA (for < 3 cm HCC)

No
Solitary tumor ≤ 5 cm
≤ 3 tumors ≤ 3 cm
No venous invasion

Child–Pugh A
Local ablation

Child–Pugh B
Transplantation

Child–Pugh C
TACE

Extrahepatic metastasis
Main portal vein tumor thrombus

Child–Pugh A/B
Child–Pugh C

Sorafenib or systemic therapy trial

Tumor > 5 cm
> 3 tumors
Invasion of hepatic / portal vein branches

Child–Pugh A/B
Supportive care

Child–Pugh C
Nation-wide Survey of HCC in Korea
- Frequency of 1st Treatment Methods in real CP-

Also much discrepancy between guidelines and real practice in Korea
Curative treatment for early stage HCC

• Surgery is the mainstay of curative treatment.
• But, high recurrence rate after surgical resection is still a problem.

Predictors of recurrence:
- Differentiation degree (p=.013)
- Multinodular HCC (p=.045)
- Satellites (p=.02)
Emerging Trends of Management in Early Stage

- Resection; Classic or Minimal invasive surgery (laparoscopic or Robot surgery)
- Liver transplantation; expansion of criteria
- Local ablation therapy; RFA, PEIT or Holmium
- Adjuvant therapy after curative tx.; molecular target therapy (phase III; STORM, PATRON),

Curative efficacy
Practice Guideline; Intermediate Stage

**Very early stage**
- Single HCC mass <2 cm
- Carcinoma in situ

  - 1 HCC
    - Portal pressure/bilirubin
      - Normal
        - Resection
        - Potentially curative treatments
      - Possible contraindication to transplant
        - NO
          - Resection
        - YES
          - Other options

**Early stage**
- 1 HCC or 3 nodules <3 cm, PS 0

  - 3 nodules ≤3 cm
    - Possible contraindication to transplant
      - NO
        - Resection
      - YES
        - Other options

**Intermediate stage**
- No portal vein thrombosis
- Multinodular, PS 0

  - Chemoembolization

**Advanced stage**
- Portal invasion, Metastases, PS 0-2

  - Sorafenib

**Terminal stage**

  - Symptomatic therapy
TACE; Effective but incomplete
Degree of lipiodol uptake determines survival in conventional TACE

Incomplete TACE induces angiogenesis

Sergio et al., Am J Gastroenterol 2007
TACE: ineffective for large or multiple (≥4) HCC

Sorafenib in Combination with TACE for Intermediate HCC

Inclusion Criteria
• Unresectable, multinodular, HCC
• Child-Pugh A without ascites or encephalopathy
• ECOG PS of 0

Exclusion Criteria
• Vasc. invasion, extrahepatic spread (VI/EHS)
• Planned liver transplantation
• Previous local therapy to target lesion
• Prior TACE, prior systemic therapy

Primary Endpoint
• Time to progression (by central review)

Secondary Endpoints
• Overall survival
• Time to VI/EHS
• Time to untreatable progression
• Safety

First TACE with DEB performed 3-7 days after start of treatment with sorafenib or placebo
• Subsequent TACE with DEB performed on day 1 (±4 days) of cycles 3, 7, and 13, and every 6 cycles thereafter
• Patients allowed optional TACE with DEB sessions between cycles 7 and 13 and cycles 13 and 19, if deemed necessary by the investigator

Adapted from Cheng presentation at AP BESTT 2012

Lencioni et al., ASCO GI 2012
TACE vs. TACE+RT: Survivals

Response rate; 65.8%

TACE vs. TACE+RT
P<0.01

14.3%
36%

Shim and Seong et al. 2005, Liver International
TACE vs. TACE+RT:
Median survival-Tumor size

Shim and Seong et al. 2005, Liver International
Radioembolization with Yttrium-90 microsphere

Ischemia

Radiation
Advanced Stage
OS in the SHARP and AP Trials

Sorafenib consistently increased overall survival in different global patient populations

**SHARP<sup>1</sup>**
- **Sorafenib (n=299)**
  - Median: 10.7 months
  - 95% CI: 9.4-13.3
- **Placebo (n=303)**
  - Median: 7.9 months
  - 95% CI: 6.8-9.1
- **HR (S/P): 0.69**
  - 95% CI: 0.55-0.87
  - *P*=0.00058

**Asia-Pacific<sup>2</sup>**
- **Sorafenib (n=150)**
  - Median: 6.5 months
  - 95% CI: 5.6-7.6
- **Placebo (n=76)**
  - Median: 4.2 months
  - 95% CI: 3.7-5.5
- **HR (S/P): 0.68**
  - 95% CI: 0.50-0.93
  - *P*=0.014

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Position of Sorafenib in advanced HCC; AP region

Pros

• Only one approved drug therapy by large scaled prospected RCT
• Less harmful oral drug for cirrhotic liver
• Is able to manage in out-patient clinic

Cons

• High cost to maintain indefinite tx
• OS in Asian patients with HCC is shorter than SHARP trial
• SAE is more common
• Not enough data in clinical practice level

Lee JM, Han KH: *Positioning and indication of sorafenib in the treatment algorithm and real practice setting: Western and eastern approach--Asian perspective*. Oncology; 2010
Emerging Trends; Treatment of Advanced HCC:

- New molecular target agents
- New combination treatment
- Exploring alternative treatment
Beyond sorafenib: novel targeted therapies for advanced HCC

- **Antiangiogenic agents**: Sunitinib, Brivanib, Linifanib (ABT-869), Bevacizumab, AZD2171 (cediranib), PTK787 (Vatalanib)

- **EGFR inhibitors**: EGFR tyrosine kinase inhibitors (erlotinib (Tarceva), Lapatinib, Monoclonal antibodies against EGFR (Cetuximab))

- **mTOR inhibitors**: (sirolimus, temsirolimus and everolimus)

- **Others**: MEK inhibitors
### Hepatic arterial infusion chemotherapy (HAIC)

<table>
<thead>
<tr>
<th>Group</th>
<th>Therapeutic Scheme</th>
<th>No. Median OS</th>
<th>1-yr survival rate</th>
<th>Objective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ando et al. 2002</td>
<td>DDP 7 mg/m², 5-FU 170 mg/m², D1-D5, 4 consecutive weeks</td>
<td>48</td>
<td>10.2 mo</td>
<td>45.0%</td>
</tr>
<tr>
<td>Itamoto et al. 2002</td>
<td>DDP 10 mg, 5-FU 250 mg, D1-D5, 4 consecutive weeks</td>
<td>7</td>
<td>7.5 mo</td>
<td>33%</td>
</tr>
<tr>
<td>Yamasaki et al. 2005</td>
<td>DDP 10 mg, 5-FU 250 mg (+ LV), D1-D5, 4 consecutive weeks</td>
<td>44</td>
<td>9.4 mo</td>
<td>39.0%</td>
</tr>
<tr>
<td>Tanioka et al. 2003</td>
<td>DDP 7 mg/m², D1-D5 5-F 170 mg/m², D1-D7, 4 consecutive weeks</td>
<td>38</td>
<td>6.0 mo</td>
<td>17.8%</td>
</tr>
</tbody>
</table>

*Llovett et al. Median OS was 10.7*
YLCSC

Medical team
- Hepatologist, oncologist
- Liver surgeon, transplant surgeon, Pathologist

Surgical team

Radiology team
- Diagnostic radiology
- Intervention radiology
- Radiation oncology
Radiation Therapy for HCC

Dose Visualization: Analysis of Isodose & DVH

Tumor
Non-tumor liver
Applicability of BCLC stage for prognostic stratification in comparison with other staging systems: single centre experience from long-term clinical outcomes of 1717 treatment-naïve patients with hepatocellular carcinoma

Beom Kyung Kim\textsuperscript{1,5,*}, Seung Up Kim\textsuperscript{1,3,5,*}, Jun Yong Park\textsuperscript{1,3,5}, Do Young Kim\textsuperscript{1,3,5}, Sang Hoon Ahn\textsuperscript{1,3,5,6}, Mi Sung Park\textsuperscript{1}, Eun Hye Kim\textsuperscript{1}, Jinsil Seong\textsuperscript{2,3,5}, Do Youn Lee\textsuperscript{3,4,5} and Kwang-Hyub Han\textsuperscript{1,3,5,6}

Fig. 1. Cumulative overall survival according to BCLC stage (from stage 0 to stage D).
## Treatment outcome of 1,717 treatment-naïve HCC (2003-8)

<table>
<thead>
<tr>
<th>BCLC Stage</th>
<th>Modality</th>
<th>n (%)</th>
<th>Median 6-MOS</th>
<th>1-YSR</th>
<th>2-YSR</th>
<th>3-YSR</th>
<th>4-YSR</th>
<th>5-YSR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage A (n=694)</strong></td>
<td>Curative</td>
<td>294 (42.4)</td>
<td>97.3</td>
<td>95.9</td>
<td>92.2</td>
<td>88.1</td>
<td>83.1</td>
<td>76.2</td>
<td>&lt;0.0001 (vs. TACE/TACI)</td>
</tr>
<tr>
<td></td>
<td>TACE/TACI</td>
<td>377 (54.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>23 (3.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage B (n=333)</strong></td>
<td>TACE/TACI</td>
<td>243 (73.0)</td>
<td>86.8</td>
<td>72.3</td>
<td>48.9</td>
<td>36.6</td>
<td>26.8</td>
<td>18.5</td>
<td>0.0003 (vs. Combined)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>39 (11.7)</td>
<td>79.5</td>
<td>56.4</td>
<td>19.2</td>
<td>9.6</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>51 (15.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage C (n=607)</strong></td>
<td>CCRT</td>
<td>74 (12.2)</td>
<td>11.3</td>
<td>67.6</td>
<td>47.3</td>
<td>24.6</td>
<td>7.2</td>
<td>7.2</td>
<td>7.2 0.5745 (vs. TACE/TACI)</td>
</tr>
<tr>
<td></td>
<td>TACE/TACI</td>
<td>213 (35.1)</td>
<td>9.0</td>
<td>66.2</td>
<td>38.9</td>
<td>23.3</td>
<td>14.4</td>
<td>10.1</td>
<td>7.3 0.0093 (vs. Systemic CTx)</td>
</tr>
<tr>
<td></td>
<td>HAIC</td>
<td>154 (25.4)</td>
<td>5.5</td>
<td>43.5</td>
<td>22.7</td>
<td>7.6</td>
<td>6.2</td>
<td>6.2</td>
<td>2.5 0.9599 (vs. Systemic CTx)</td>
</tr>
<tr>
<td><strong>Systemic CTx</strong></td>
<td>37 (6.1)</td>
<td>4.3</td>
<td>30.6</td>
<td>19.1</td>
<td>12.7</td>
<td>12.7</td>
<td>6.4</td>
<td>6.4</td>
<td>0.0001 (vs. Supportive)</td>
</tr>
<tr>
<td><strong>Supportive</strong></td>
<td>89 (14.7)</td>
<td>1.8</td>
<td>14.6</td>
<td>5.6</td>
<td>3.4</td>
<td>1.1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>40 (6.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without M1</td>
<td>503 (82.9)</td>
<td>7.4</td>
<td>55.4</td>
<td>34.7</td>
<td>19.2</td>
<td>12.4</td>
<td>10.3</td>
<td>7.9</td>
<td>0.0019</td>
</tr>
<tr>
<td>With M1</td>
<td>104 (17.1)</td>
<td>4.3</td>
<td>38.5</td>
<td>21.0</td>
<td>10.5</td>
<td>8.9</td>
<td>4.5</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>
Pilot Clinical Trial of Localized Concurrent Chemoradiation Therapy for Locally Advanced Hepatocellular Carcinoma With Portal Vein Thrombosis

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³ Department of Diagnostic Radiology, Yonsei Liver Cancer Special Clinic, Yonsei Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea.

Han & Seong et al. 2008, Cancer
 Converted to Resection after CCRT

M/51, 16 cm, T4N0, PVT

1 mo

15 mo, path: 100%

M/53, 11 cm, T3N0

Initial

post-CCRT

pre-OP
Comparison of 5 year survival rates of cancer in Korea (1993-2008)

Source: Ministry of Health & Welfare, The Korea Central Cancer Registry, 2010
Summary; Optimal treatment in HCC

• Early diagnosis is the most important issue to improve survival
• There are many options according to stage and treatment response.
• Try to avoid incomplete treatment
• Multidisciplinary team approach is essential.
Thank You for your attention!
The 4th Asia-Pacific Primary Liver Cancer Expert Meeting

A Bridge to a Consensus on HCC Management

July 5-7, 2013
Paradise Hotel Busan
Busan, Korea

Hosted by
The Korean Liver Cancer Study Group

Organized by
The Organizing Committee of The Asia-Pacific Primary Liver Cancer Expert Meeting

Endorsed by
- The Korean Association for the Study of the Liver
- The Liver Cancer Study Group of Japan
- Chinese Society of Hepatology

www.applecongress.org
Combination of conventional LRTs (TACE, HAIC, or CCRT) with sorafenib in advanced HCC

- Median OS and PFS is significantly longer of S-LRTs than S-M.

(A) Overall Survival (OS) of entire cohort

S-LRT
Median OS 8.5 month
95% CI 6.2-10.7

S-M
Median PFS 5.5 month
95% CI 4.7-6.2

P=0.001

(B) Progression free survival of entire cohort

S-LRT
Median PFS 5.3 month
95% CI 4.0-6.5

S-M
Median PFS 3.0 month
95% CI 2.7-3.2

P=0.002

Han et al. 2012….
Repetitive Short-Course Hepatic Arterial Infusion Chemotherapy With High-Dose 5-Fluorouracil and Cisplatin in Patients With Advanced Hepatocellular Carcinoma

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Sang Hoon Ahn, MD1,2
Young Joon Yoon, MD1,2
Ja Kyung Kim, MD1,2
Hyun Woong Lee, MD1,2
Do Yun Lee, MD2,3
Chae Yoon Chon, MD1,2
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BACKGROUND. Hepatic arterial infusion chemotherapy (HAIC) has often been selected as a therapeutic option for patients with advanced hepatocellular carcinoma (HCC). The objective of the current study was to evaluate the efficacy and safety of repetitive HAIC with high-dose 5-fluorouracil (5-FU) and cisplatin given for 3 days in patients with advanced HCC.

METHODS. Between January 2001 and December 2004, a total of 41 patients with unresectable advanced HCC were enrolled. The patients underwent HAIC via the implantable port system with 5-FU (at a dose of 500 mg/m² on Days 1–3) and cisplatin (at a dose of 60 mg/m² on Day 2) every 4 weeks. Tumor response was assessed at the end of every 3 cycles.

RESULTS. The median age of the patients was 53 years and 34 patients (82.9%) had evidence of portal vein thrombosis. In total, 230 cycles of HAIC were administered to the 41 patients, with a median of 6 cycles given (range, 1–14 cycles). Nine patients (22.0%) achieved a partial response and 14 patients (34.1%) had stable disease. The median time to disease progression and overall survival were 7.0 months and 12.0 months, respectively. The overall survival was found to be significantly longer in the successful disease control group (patients with a complete response, partial response, and stable disease) than in the disease progression group (median of 14.0 months vs 6.0 months; P < .001). Adverse reactions were tolerable and successfully managed with conservative treatment.

CONCLUSIONS. HAIC with high-dose 5-FU and cisplatin given for 3 days achieved effective and safe results in patients with advanced HCC. Therefore, repetitive short-course HAIC with high-dose 5-FU and cisplatin may be useful as an alternative therapeutic option for patients with advanced HCC. Cancer 2007;110:129–37. © 2007 American Cancer Society.