Current Management of Intermediate HCC: Unmet Medical Needs

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BCLC Staging and Treatment Algorithm

**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
- Early stage (A)
  - Single or 3 nodules ≤3 cm
- Intermediate stage (B)
  - Multinodular PS 0
- Advanced stage (C)
  - Portal invasion, N1, M1, PS 1–2

**Stage D**
- Okuda 3, PST <2, Child-Pugh C
- Terminal stage (D)
  - Symptomatic (20%)
  - Survival <3 months

**Unresectable disease**
- Randomised controlled trials (RCTs) (50%)
  - 3-year survival: 10–40%
- Sorafenib
- TACE
- RFA
- Liver transplantation (CLT/LDLT)
- Resection

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

TACE for Intermediate HCC

- **Vascular invasion**: Barcelona: 0%; Hong Kong 27%
- **2-year OS of untreated group**: Barcelona: 27%; Hong-Kong 11%

![Graph showing probability of survival](image)

- Chemoembolisation
- Control

P = 0.009  
P = 0.002

TACE for HCC

Lipiodol-TACE with cisplatin or doxorubicin

484 patients (1989 - 1997)
- Response rate: 50%
- Morbidity: 23%
- TACE-related Mortality: 4%
- Survival: 1-yr 49%, 3-yr 23%, 5-yr 17%
- Adverse prognostic factors:
  - tumor size > 10 cm,
  - serum albumin < 35 g/L

Unmet Needs in Intermediate Stage HCC

- Can we improve results of TACE by better technologies or combination with systemic therapy?

- Is cure possible for intermediate stage HCC by more aggressive treatments such as resection or ablation?
Objective response rate 70% by modified RECIST criteria


TACE with Drug-Eluting Beads – Is It a Significant Improvement?

Phase ½ trial of doxorubicin eluting for HCC:
Randomized Controlled Trial of DEB-TACE vs. cTACE

European multi-centre randomized trial to compare safety and efficacy of doxorubicin-eluting bead with conventional TACE using Lipiodol-doxorubicin (100 patients in each arm)

Doxorubicin-Related Side Effects

Gastrointestinal and Liver Serious Adverse Events (SAEs)

Malagari et al. Cardiovasc Intervent Radiol 2010
Overall 6-Month Tumour Response Rates

No significant difference in objective response rate
Combining TACE with Sorafenib

Primary endpoint: TTP by central review

- Sorafenib (n=229)
  - Median: 5.4 months
  - (95% CI: 3.8–7.2)
- Placebo (n=229)
  - Median: 3.7 months
  - (95% CI: 3.5–4.0)

HR (S/P) = 0.87
95% CI: 0.70–1.09
P = 0.252 (two-sided)

Patients at risk
- Sorafenib: 229
  - 69, 33, 15, 1, 0, 0
- Placebo: 229
  - 70, 47, 21, 6, 1, 0

<table>
<thead>
<tr>
<th>Outcome, median months</th>
<th>Sorafenib (n=229)</th>
<th>Placebo (n=229)</th>
<th>HR (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP by central review^a</td>
<td>5.4</td>
<td>3.7</td>
<td>0.87 (0.252)</td>
</tr>
<tr>
<td>TTP by investigator^b</td>
<td>7.2</td>
<td>5.3</td>
<td>0.79 (0.049)</td>
</tr>
<tr>
<td>OS</td>
<td>29.7</td>
<td>Not reached</td>
<td>1.06 (0.790)</td>
</tr>
</tbody>
</table>

^aPrimary endpoint; ^bExploratory analysis
CI = confidence interval; HR = hazard ratio

SPACE Trial (Concurrent Sorafenib + TACE)

- **Lencioni R, et al. ASCO GI 2012:abstract LBA154**

### Progression-free probability

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at risk</td>
<td>Median: 169 days</td>
<td>Median: 166 days</td>
</tr>
<tr>
<td></td>
<td>95% CI: 166, 219 days</td>
<td>95% CI: 113, 168 days</td>
</tr>
<tr>
<td>HR</td>
<td>0.797</td>
<td>0.797</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.588–1.08</td>
<td>0.588–1.08</td>
</tr>
<tr>
<td>P-value</td>
<td>0.072</td>
<td>0.072</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Sorafenib</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>86</td>
<td>91</td>
</tr>
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<td></td>
<td>33</td>
<td>33</td>
</tr>
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<td></td>
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<td>12</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
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</table>
BCLC is Conservative in Treatment Recommendation for Intermediate Stage HCC

Many clinicians especially in the East consider that:

• Role of surgical resection can be extended to intermediate HCC

• Role of ablation can be extended to larger tumors > 3 cm, or even > 5 cm
Extrahepatic metastasis
Main portal vein tumor thrombus

Solitary or multifocal tumor in noncirrhotic liver or Child A cirrhosis

Yes
Resection / RFA (for < 3 cm HCC)

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

Child A

Child B

Child C

Local ablation
Transplantation

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

Child A / B

Child’s C

TACE
Supportive care

Sorafenib or systemic therapy trial

APASL Consensus on Treatment of HCC

Omata et al. Hepatol Int 2010
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.
Hong Kong Liver Cancer Staging System

- Tumors in the liver classified into early, intermediate and advanced based on 0, 1 or ≥ 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>≤ 5 cm</td>
<td>≤ 3</td>
<td>No</td>
</tr>
<tr>
<td>Intermediate</td>
<td>≤ 5 cm</td>
<td>≤ 3</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>≤ 5 cm</td>
<td>&gt; 3</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 cm</td>
<td>≤ 3</td>
<td>No</td>
</tr>
<tr>
<td>Locally-advanced</td>
<td>≤ 5 cm</td>
<td>&gt; 3</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 cm</td>
<td>≤ 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

HCC

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

ECOG 2-4
Child C

EVM*

Early tumor
Stage 5a
Liver Transplantation

Intermediate/advanced tumors
Stage 5b
Supportive care

Systemic therapy

*EVM, extrahepatic vascular invasion/metastasis
Comparison of HKLC and BCLC Staging System

When patients received treatment according to the HKLC algorithm, the median OS time of these patients would be 16.6 months, in contrast to 8.9 months when they received treatment according to the BCLC algorithm.

Hypothetical Kaplan–Meier estimated overall survival curves of the HKLC scheme and the BCLC scheme. The survival data of patients who were not treated with HKLC-recommended treatments were substituted by a random draw from the group of patients who had a similar prognosis and were treated according to HKLC recommendations. The BCLC curve was created in a similar way.
Of BCLC-B patients classified as HKLC-II, the survival benefit of radical therapies (*resection or RFA*), compared with TACE, was substantial (5-year survival, 52.1% vs 18.7%; P < .0001)
Resection for Multifocal HCC
Survival of Patients with Multiple Tumors – QMH Experience 2000-2011

5-yr disease-free survival after resection of multifocal HCC 21%
Resection for BCLC Stage B HCC - An East-West Multicenter Study

2046 patients with HCC resection studied: 746 (36%) from the 3 Asian centers; 307 (15%) from the 3 American centers; and 993 (49%) from the 4 European centers

- 1012 (50%) were BCLC 0-A (451 from the eastern centers and 561 from the western centers), 737 (36%)* BCLC B (226 from the eastern centers and 511 from the western centers), and 297 (14%) BCLC C (69 from the eastern centers and 228 from the western centers)

Survival after Resection by BCLC classification

Overall operative mortality 2.3% (BCLC A 1.6%, B 3.1% and C 2.5%)

Overall 5-yr survival 56% (BCLC A 61%, B 57% and C 38%)

5-yr disease-free survival: BCLC A 31%, B 27%, C 18%)
Combined Resection and Ablation
Overall Survival Results

Combined treatment vs. resection alone

- No hospital mortality in both groups
- Median survival: 53.0 vs. 44.5 months

Cheung et al. World J Gastroenterol 2010
## Long-term Results of RFA for HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Mean/Median FU (m)</th>
<th>Recurrence rate</th>
<th>5-year survival</th>
<th>5-year disease-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossi 1996</td>
<td>39</td>
<td>22.6</td>
<td>41%</td>
<td>40%</td>
<td>NA</td>
</tr>
<tr>
<td>Lencioni 2005</td>
<td>187</td>
<td>24</td>
<td>50%</td>
<td>48%</td>
<td>NA</td>
</tr>
<tr>
<td>Machi 2005</td>
<td>65</td>
<td>24.8</td>
<td>57%</td>
<td>40%</td>
<td>28%</td>
</tr>
<tr>
<td>Cabassa 2006</td>
<td>59</td>
<td>24.1</td>
<td>58%</td>
<td>43%</td>
<td>17% (3-year)</td>
</tr>
<tr>
<td>Choi 2007</td>
<td>570</td>
<td>30.7</td>
<td>52%</td>
<td>58%</td>
<td>NA</td>
</tr>
<tr>
<td>Ng 2008</td>
<td>207</td>
<td>26</td>
<td>81%</td>
<td>42%</td>
<td>28%</td>
</tr>
</tbody>
</table>
Local Recurrence after RFA for HCC

- Incomplete necrosis of tumor cells in ablated lesion
  - Complete necrosis only in 29 of 38 (83%) tumors ablated by RFA followed by liver transplantation based on histological examination of explants

  Lu et al. Radiology 2005

- Untreated microsatellite nodules adjacent to tumor

- Risk factors of local recurrence by meta-analysis of 5224 liver tumors treated by RFA from 95 series in the literature:
  - tumor size > 3 cm (p< 0.001)
  - percutaneous vs. surgical approach (p< 0.001)

Role of RFA for Large HCC > 5 cm

• Percutaneous RFA for HCC > 5 cm:
  Complete ablation rate < 50%
  (compared with 90% for HCC < 3 cm)
  Livraghi et al, Radiology 2000
  Guglielmi et al, Hepatogastroenterology 2003

• Open RFA for HCC > 5 cm:
  Complete ablation rate 83% (vs. 96% for HCC < 3 cm)
  Poon et al, Arch Surg 2004
Reducing Recurrence after RFA

- ThermoDox® (doxorubicin encapsulated in heat-activated liposome)
Mode of Action for ThermoDox

• Local tissue concentration ≈ 10x that of standard free doxorubicin, higher cancer cytotoxicity and reduced systemic toxicity

• Direct toxicity to tumor vasculature

Synergistic effects

• Cytotoxic effect enhanced by heat (doxorubicin binding to tumor DNA)

• Reduction of ablation threshold temperature – enhanced lesion size
RF Ablation / ThermoDox Combination

Micro-metastases outside the ablation zone “kill” area. These are a potential site of recurrence if not treated.

Ablated Tumor and 1 cm “Tumor-Free” Margin

High concentration of doxorubicin deposited by ThermoDox in this thermal zone.
Phase I Study of Thermodox at NCI (USA) and QMH (HK)

• A total of 24 patients were treated (3, 6, 6, 6, 3 patients at doses of 20, 30, 40, 50 and 60 mg/m², respectively)

• Median tumor size 3.7 cm (range 1.7-6.5 cm), and totally 28 tumors treated

• The MTD was determined in this study as 50 mg/m²

• No severe adverse events (grade 1 alopecia, transient neutropenis)

• Complete ablation rate 88%; enlarged ablation zone

Brad & Poon, Clin Cancer Res 2010
Eligibility:
- non-resectable HCC
- no more than 4 lesions
- at least 1 lesion > 3cm and none > 7cm
- no previous treatment
- Child-Pugh A or B

Stratification
- lesion size: 3-5 vs >5-7 cm and RFA technique:
  - open surgical
  - laparoscopic or
  - percutaneous

End Points:
Primary: PFS (Progression Free Survival)
designed to show a 33% improvement in PFS with 80% power and a p-value = 0.05

Secondary: OS (Overall Survival), TTLR (time to local recurrence), Safety
Results of HEAT Study

- ThermoDox® in combination with RFA did not meet the primary endpoint of the Phase III HEAT Study in patients with HCC; ThermoDox® was well-tolerated with no unexpected serious adverse events.

- Greatest benefit in patients that had RFA > 45 mins
  - Single lesion patients (65% of population)
  - Consistent in both PFS & OS analysis
Post Hoc Analysis

- Ablation time or strategy was not mandated in HEAT Study
  - High degree of variability exists with ablation cycles and treatment time by lesion size

- Recent simulation studies show that prolonged heating > 45 min. is required in order to achieve optimal tissue concentrations of doxorubicin

- Patients with single lesion with optimized RFA duration may be the best strategy
Overall Survival Subgroup Analysis
Patients with RFA ≥ 45 mins. (n=285 patients)

HR = 0.63  (95% CI 0.43– 0.93)
P-Value = 0.0198

Median Survival –July 15, 2015
RFA plus Thermodox – 79.0 mo.
RFA alone – 53.6 mo.
Conclusions

• More aggressive treatment of HCC including resection and RFA may lead to improved long-term survival and possible cure in patients with intermediate stage HCC

• TACE remains mainstay of palliative treatment for intermediate HCC in patients whose liver function reserve is not adequate for surgical treatment - but little improvement over the past three decades

• Need for effective combination strategy to further improve long-term outcome of patients with intermediate HCC
08 – 10 July 2016 (Friday – Sunday)
Crowne Plaza Hotel Hong Kong

applecongress2016.org