Treatment of Hepatocellular carcinoma: state of the art

The 2nd World Congress on Controversies in the Management of Viral Hepatitis (C-Hep) Berlin, Germany October 18-20, 2012
Treatment of Hepatocellular Carcinoma: state of the art

- EASL EORTC & AASLD guidelines
- Critical areas in clinical decision making on HCC
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Table 4. Ongoing randomized phase II–III trials aimed to change the standard of care in HCC management during the period 2012–13.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Randomized studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>1. Sorafenib vs. placebo</td>
</tr>
<tr>
<td>Intermediate HCC</td>
<td>1. Chemoembolization ± sorafenib</td>
</tr>
<tr>
<td></td>
<td>2. Chemoembolization ± brivanib</td>
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<tr>
<td></td>
<td>3. Chemoembolization ± everolimus</td>
</tr>
<tr>
<td>Advanced HCC</td>
<td></td>
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<tr>
<td>First line</td>
<td>1. Sorafenib ± erlotinib</td>
</tr>
<tr>
<td></td>
<td>2. Sorafenib vs. brivanib</td>
</tr>
<tr>
<td></td>
<td>3. Sorafenib vs. sunitinib*</td>
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<tr>
<td></td>
<td>4. Sorafenib vs. linifanib**</td>
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<tr>
<td></td>
<td>5. Sorafenib ± Yttrium-90</td>
</tr>
<tr>
<td></td>
<td>6. Sorafenib ± doxorubicin</td>
</tr>
<tr>
<td>Second line</td>
<td>1. Brivanib vs. placebo**</td>
</tr>
<tr>
<td></td>
<td>2. Everolimus vs. placebo</td>
</tr>
<tr>
<td></td>
<td>3. Ramucirumab vs. placebo</td>
</tr>
</tbody>
</table>

*Halted 2010 for futility/toxicity.
**See addendum at the end of the Guidelines.
Refinement of BCLC classification

• **BCLC B & C stage** patients [Huitzil-Melendez, 2010]
  • Large range of survival
    • B (45-11 mo) and C (11-5 months) is quite large
  • Large range of responses to a given treatment
  • Further stratification of patients within each class should be explored
    • Liver function (Child–Pugh A versus B, or ascites)
    • Prognostic variables (ECOG, cancer invasiveness)
    • Prognostic molecular biomarkers
Molecular classification of HCC (1)

- to understand biological subclasses and drivers of the disease,
- to optimize benefits from molecular therapies
- to enrich trial populations

[breast cancer: Her2/neu status discriminates outcome and treatment response to trastuzumab; Slamon 2001]
[EGFR mutational status in NSCLC identifies the responders to TKIs; Tsao 2005]
[melanoma patients with BRAF mutations respond to B-RAF inhibitors; Flaherty 2010]

In HCC, no molecular subclass has been reported as responding to specific targeted therapy
Hepatocellular Carcinoma
(“signaling pathways” and “nuclear effectors”)

**PROLIFERATION / SURVIVAL**
EGF
IGF
MET
Akt/mTOR
Raf/Raf/MAPKs
Hippo (YAP, Mst1/2, Lats1/2)

**INFLAMMATION**
IFN
IL6
JAK / STATs

**CELL DIFFERENTIATION / EMT**
WNT
TGF-b
Sonic/Hedgehog
Notch

**ANGIOGENESIS**
VEGF
FGF
PDGF

**NUCLEAR EFFECTORS**
p53 family
β-catenin
E2Fs
c-Jun
CREB / ATFs

**miRNAs**
Molecular classification of HCC (4)

Molecular classification of HCC based on gene signatures or molecular abnormalities is not ready for clinical application (evidence 2A; recommendation 1B)
Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma

Riccardo Lencioni, M.D.,¹ and Josep M. Llovet, M.D.²,³

Conventional RECIST: longest overall tumor diameter

mRECIST: longest viable tumor diameter

Key Messages

- BCLC staging system is recommended for prognostic prediction and treatment allocation and mRECIST is the best method to classify treatment response.

- Molecular classification of HCC based on gene signatures or molecular abnormalities is not ready for clinical application.
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• EASL EORTC & AASLD guidelines
• Critical areas in clinical decision making on HCC
Critical area in clinical decision making for HCC

AASLD PRACTICE GUIDELINE 2010
MANAGEMENT OF HEPATOCELLULAR CARCINOMA: AN UPDATE
Jordi Bruix and Morris Sherman

EASL–EORTC CLINICAL PRACTICE GUIDELINES 2012
MANAGEMENT OF HEPATOCELLULAR CARCINOMA

Chairmen: Josep M. Llovet (EASL); Michel Ducreux (EORTC).
Clinical Practice Guidelines Members: Riccardo Lencioni; Adrian M. Di Bisceglie; Peter R. Galle; Jean Francois Dufour; Tim F. Greten; Eric Raymond; Tania Roskams; Thierry De Baere; Michel Ducreux; and Vincenzo Mazzaferro.
EASL Governing Board Representatives: Mauro Bernardi
Reviewers: Jordi Bruix; Massimo Colombo; Andrew Zhu

PRACTICAL RECOMMENDATIONS FOR THE MULTIDISCIPLINARY APPROACH TO THE TREATMENT OF HEPATOCELLULAR CARCINOMA 2012
The Italian Association for the Study of the Liver (A.I.S.F.)

AISF Expert panel: Luigi Bolondi, Matteo Cescon, Umberto Cillo, Massimo Colombo, Antonio Craxì, Fabio Farinati, Edoardo Giovanni Giannini, Rita Golfieri, Massimo Levrero, Fabio Piscaglia, Giovanni Raimondo, Franco Trevisani
AISF Coordinating Committee: Paolo Caraceni, Barbara Coco, Alessia Ciancio, Mirella Fraquelli, Maria Rendina, Giovanni Squadrito
Updated BCLC staging system and treatment strategy

HCC

Stage 0
PST 0, Child–Pugh A

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

Early stage (A)
1 HCC or 3 nodules < 3 cm, PST 0

Intermediate stage (B)
Multinodular, PST 0

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

Stage D
PST > 2, Child–Pugh C

End stage (D)

Resection
Liver transplantation
PEI/RFA
TACE
Sorafenib
Best supportive care

Curative treatments (30%)
5-year survival (40–70%)
Target: 20%
OS: 20 mo (45-14)
Target: 40%
OS: 11 mo (6-14)
Target: 10%
OS: <3 mo

One stage one treatment: combination treatment? Second line treatment?

**Critical area in clinical decision making for HCC**

**Staging**

**BCLC staging system limitations (1)**

- univocal treatment option for each stage
- absence of indications regarding second-line or combined/sequential treatments

- assignment to the advanced stage (BCLC C) of all patients with a PS 1
- assignment to the terminal stage (BCLC D) of patients with small tumors in Child-Pugh class C, whereas they most benefit from LT [Berry, 2012; Cillo, 2010; Vitale 2011; Merani, 2011]
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- BCLC staging might have some limitation (Usage of PST in cirrhotic patients, LT in CP stage C, consideration for 2° line & combination treatment)
Updated BCLC staging system and treatment strategy

- **Stage 0**: PST 0, Child–Pugh A
  - Very early stage (0)
    - 1 HCC < 2 cm
    - Carcinoma in situ
  - Early stage (A)
    - 1 HCC or 3 nodules < 3 cm, PST 0
  - Intermediate stage (B)
    - Multinodular, PST 0

- **Stage A–C**: PST 0–2, Child–Pugh A–B
  - Advanced stage (C)
    - Portal invasion, N1, M1, PST 1–2
  - End stage (D)
    - PST > 2, Child–Pugh C

- Associated diseases
  - Yes
  - No

- **PST 0-1**
  - Increased
  - Associated diseases

- Treatment options
  - Resection
  - Liver transplantation
  - PEI/RFA
  - TACE
  - Sorafenib
  - Best supportive care

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

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

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

**Target: 10%**
- OS: <3 mo

Results of RF and resection in patients with very early HCC (single <2 cm)

Propensity analysis (resection 52 vs RF 91→52)

One-to-one near-neighbor matching for:
sex, age, HBsAg, anti-HCV, platelet, Child-Pugh, AFP, ALT, BMI, hypertension, diabetes.

RF has:
- Negligible mortality
- Lower liver mutilation
- Lower costs
- Shorter hospital stay
- Easy repeatability

Wang JH et al., J Hepatol 2011 [Epub ahead of print]
In compensated cirrhosis, **first-line RF** (followed by resection if failure) **is better than resection** (followed by RF for recurrence) if:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Threshold</th>
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<tbody>
<tr>
<td>Median survival (in years) of progressive HCC</td>
<td>&gt; 2.73</td>
</tr>
<tr>
<td>Probability of perioperative mortality</td>
<td>&gt; 1.0%</td>
</tr>
<tr>
<td>Probability of local recurrence following RFA</td>
<td>&lt; 1.9%</td>
</tr>
<tr>
<td>Probability of positive microscopic resection margin</td>
<td>&gt; 0.28%</td>
</tr>
<tr>
<td>Probability of performing RFA for recurrent HCC</td>
<td>&gt; 70.2%</td>
</tr>
</tbody>
</table>
Critical area in clinical decision making for HCC Treatment

Ablation techniques

• For HCC ≤2 cm, RFTA = first-line treatment ?
  • similar survival rates,
  • lower morbidity and mortality,
  • shorter hospital stay, and
  • lower sanitary costs)

• For HCC of 2.1-3 cm, choice between surgery and on a case-by-case multi-disciplinary evaluation
  [“rescue” resection after of incomplete HCC necrosis with RFTA offers a survival chance equivalent to that of patients treated with surgery as first-line approach [Cho, 2010]

• In patients not suitable to a percutaneous approach, ablation can be performed through the video-laparoscopic route, resulting a safe and efficacious method
Is Portal Hypertension a Contraindication to Hepatic Resection?

Alessandro Cucchetti, MD,* Giorgio Ercolani, MD,* Marco Vivarelli, MD,* Matteo Cescon, MD,* Matteo Ravaioli, MD,* Giovanni Ramacciato, MD,† Gian Luca Grazi, MD,* and Antonio Daniele Pinna, MD*

Annals of Surgery • Volume 250, Number 6, December 2009

P=0.008

241 pts.

156 pts.
Eligibility for Liver resection
BLOG algorithm

Cirrhotic patient eligible for liver resection

MELD score

<9

≥ 140 mEq/L
Major hepatectomy (up to 4 segments)

< 140 mEq/L
Segmentectomy or bisegmentectomy

9 - 10

Serum sodium level

>10

Risk of IPLF >15% in all types of hepatectomy

Mortality

0 - 3.3%
0
0 – 2.5%
Critical area in clinical decision making for HCC Treatment

Surgical Resection (1)

The size of the nodule ("single large HCC") has a lesser prognostic impact for resection than for loco-regional therapies [Minagawa, 2007; Shifman, 2010; Yang, 2009]

• Surgical resections is the only available radical treatment for single HCC >5 cm. Always assess its feasibility, preferably in a multidisciplinary setting (3b-B)
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• Usage of RFT as first line in stage 0 and extension of indications for surgical resection could be considered on a case by case basis by a multidisciplinary approach
Updated BCLC staging system and treatment strategy

Stage 0
PST 0, Child–Pugh A

- Very early stage (0)
  - 1 HCC < 2 cm
  - Carcinoma in situ

Stage A–C
PST 0–2, Child–Pugh A–B

- Early stage (A)
  - 1 HCC or 3 nodules
  - < 3 cm, PST 0

- Intermediate stage (B)
  - Multinodular
  - PST 0

Stage D
PST > 2, Child–Pugh C

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

End stage (D)

HCC

1 HCC
Portal pressure/bilirubin

Increased
No
Yes

Portal pressure/bilirubin

Normal

Associated diseases

1 HCC

3 nodules ≤ 3 cm

Resection
Liver transplantation
PEI/RFA
TACE
Sorafenib
Best supportive care

Curative treatments (30%)
5-year survival (40–70%)
Target: 20%
OS: 20 mo (45-14)
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Combined Locoregional Treatments

Comparison N. trials:

- TACE + PEI vs. TACE
  - 4 trials
- TACE + RF vs. RF
  - 2 trials
- TACE + PEI vs. PEI
  - 1 trial
- TACE + RF vs. TACE
  - 1 trial
- TACE + RF vs. TACE o PEI
  - 1 trial
- TACE + RF vs. TACE o RF
  - 1 trial

Survival at:

- 1 yr: 512 pts. → OR = 3.26 (95% CI = 1.23-8.69)
- 2 yrs: 437 pts. → OR = 4.53 (95% CI = 2.62-7.82)
- 3 yrs: 425 pts. → OR = 3.50 (95% CI = 1.75-7.02)

Recurrence rate

Wang W et al., Liver International 2010; 30: 741-749
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• In non surgical cases a combined approach could be considered
Proposed algorithm for TACE in patients with intermediate-stage HCC

Patient / disease characteristics

- No PVT
- No EHS
- Child-Pugh A or B7

First TACE

- CT or MRI
- Liver deterioration or major complications

Second TACE

- CT or MRI
- Disease progression
  - New lesion
  - Growth of existing lesion
  - Consider sorafenib

Disease control (CR or PR or SD)

Follow-up / 3 months

- Consider retreatment with TACE

- Why?

Segmental or intratumoral thrombosis?

Acceptable?

Why?

Acceptable?

Radioembolization for HCC
Patient outcomes according to tumor stage

Intermediate stage

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Author(s) and Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACE</td>
<td>Salem, Gastro. 2011</td>
</tr>
<tr>
<td>TACE</td>
<td>Wang, Eur J Cancer. 2008</td>
</tr>
<tr>
<td>TACE</td>
<td>Chen, Eur J Cancer. 2009</td>
</tr>
<tr>
<td>TARE</td>
<td>Hilgard, Hepatology. 2010</td>
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<tr>
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<tr>
<td>TARE</td>
<td>Sangro, Hepatology. 2011</td>
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Median overall survival (months)

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• Usage of RFT as first line in stage 0 and extension of indications for surgical resection could be considered on a case by case basis by a multidisciplinary approach
• In non surgical cases a combined non surgical aproach could be considered
• TACE could be considered in patients with peripheral, segmental or intratumoral thrombosis on a case by case basis
• MRI is the preferred method to assess response to TACE, but equivalent to TC for Drug Eluting Beads-TACE
• Additional TACE could be considered on a”on demand” basis (not repeated in pts with CR)
• TARE could be considered in patients with tumoral lobar portal vein branches thrombosis
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• Usage of RFT as first line in stage 0 and extension of indications for surgical resection could be considered on a case by case basis by a multidisciplinary approach
• In non surgical cases a combined approach could be considered
• TACE could be considered in patients with peripheral, segmental or intratumoral thrombosis on a case by case basis
• MRI could be the preferred method to assess response to TACE (no DEB TACE)
• Additional TACE could be considered on a”on demand” basis (not repeated in pts with CR) and TARE for pts with tumoral portal branch thrombosis