HepatoCellular Carcinoma: State of the Art

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Conflicts of interest

- Consultant, advisory role:
  - Bayer SP
  - BMS
  - Taiho
  - BTG
HCC: epidemiology

- HCC: 5th most common cancer worldwide,
  2nd most common cause of cancer death;
- Male predominance 2 / 1;
- > 80% in less developed regions of the world;
- Increase in incidence \(^1,^2\);
- In the USA: incidence will continue to rise until > 2030.

HCC: well known risk factors

- Cirrhosis: >80% of the cases\(^1,2\)
- Viral Hepatitis >80% worldwide\(^3\)
  - HBV: Asia, Africa, Latin America \(^3\)
  - HCV: Japan, Europe & USA \(^3\)
- Other \(^2,4\)
  - Alcohol +++
  - Aflatoxin B
  - Haemochromatosis, Auto-immune Hepatitis,
  - **NASH**, obesity, diabetes: HCC before cirrhosis!!!
- HCC incidence among Pts with cirrhosis: 2 – 4% per year \(^5\)

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Surveillance for HCC in cirrhosis

- Patients at high risk should be entered into surveillance program:
  - By abdominal ultrasound every 6 months\(^1\), experienced radiologist
  - Interest of AFP\(^2\) ???
  - High risk patients \(^1\):
    - Cirrhotic patients, Child-Pugh A & B;
    - Stage C awaiting liver transplantation;
    - Non cirrhotic HBV carriers, with active hepatitis, or familial history of HCC;
    - Non cirrhotic patients with chronic hepatitis C and fibrosis F3;

2. EASL-EORTC guidelines J Hepatol 2012
Diagnosis: based on medical imaging: multiphasic CT or multiphasic MRI

Fig. 1. Algorithm for investigation of small nodules found on screening in patients at risk for HCC (MDCT = multidetector CT scan).
Although the recommendations for investigation of screen-detected lesions in the liver were developed for use in patients with cirrhosis, they apply equally well to patients with chronic hepatitis B who may not have fully developed cirrhosis. In both situations, the pre-test probability of HCC being present is high. For nodules detected in an otherwise normal liver, the pre-test probability of HCC is much lower and the guidelines do not apply.
The BCLC staging system is recommended for prognostic selection and treatment assignment.

- **Very early stage (0)**: Single <2cm, Child-Pugh A, PS 0
  - Potential candidate for liver transplantation

- **Early stage (A)**: Single or ≤3 nodules <3cm, Child-Pugh A–B, PS 0
  - Single ≤3 nodules
  - Portal pressure
  - Biliubin
  - Normal
    - Ablation
    - Resection
    - Transplant
  - Increased
    - Associated diseases
      - No
        - Ablation
      - Yes
        - TACE

- **Intermediate stage (B)**: Large multinodular, Child-Pugh A–B, PS 0
  - Advanced stage (C): Portal invasion, Extrahepatic spread, Child-Pugh A–B, PS 1–2
  - Terminal stage (D): Child-Pugh C, PS 3–4

- **Palliative treatments**
  - TACE
  - Sorafenib
  - BSC
Early and very early stages
1a – surgery: resection

• Surgical resection: theoretically
  – One lesion, < 5 cm,
  – or larger but without invasive profile in asymptomatic patient,
  – No portal hypertension (Plat > 100 G/L), no hyperbilirubinemia,
  – And good (or correct) liver function,
  – Anatomical resection.

• Results:
  – Mortality <5% (2 – 3%)
  – 5 years OS = 60–70%
  – But high recurrence rate (60 - 70% at 5 years)

• No validated adjuvant treatment : TACE, sorafenib (STORM)

• But too restrictive, in real live, > 50% are above…
Early and very early stages 1b – surgery: liver transplantation

• Milan criteria
  – One lesion ≤ 5cm ou up to 3 nodules ≤3cm;
  – One year mortality ≤ 10%
  – 5 years OS = 70%

• But:
  – Organ shortage,
  – AND
  – Criteria too stricts:
    • UCSF,
    • Canada,

  up-to-seven criteria, without microvascular invasion

Early and very early stages
1b – surgery: liver transplantation

The AFP model: in use in France

<table>
<thead>
<tr>
<th>Variables</th>
<th>β coefficient</th>
<th>Hazard ratio</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest diameter, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3–6</td>
<td>0.272</td>
<td>1.31</td>
<td>1</td>
</tr>
<tr>
<td>&gt;6</td>
<td>1.347</td>
<td>3.84</td>
<td>4</td>
</tr>
<tr>
<td>Number of nodules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥4</td>
<td>0.696</td>
<td>2.01</td>
<td>2</td>
</tr>
<tr>
<td>AFP level, ng/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>100–1000</td>
<td>0.668</td>
<td>1.95</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>0.945</td>
<td>2.57</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE. The score is calculated by adding the individual points for each obtained variable. A cut-off value of 2 separates between patients at high and low risk of recurrence. In this simplified version, a cut-off value of 2 selected exactly the same patients as the original Cox score cut-off value of 0.7.

Cut-off value = 2
Low-risk ≤ 2
High-risk > 2

Early and very early stages 1b – surgery: liver transplantation

• Patients awaiting liver transplantation:
  – No treatment, but observation with imaging follow-up
  – If waiting list > 6 mo: bridging to transplant
    • TACE ? RE ? RFA ? Resection ?

• Down-staging policies for HCC exceeding criteria:
  – If down staging successful: consider transplantation;
  – Optimal treatment for down-staging: ?
  – What waiting period after down-staging: ?
  – Living donor transplantation ?

2. EASL-EORTC guidelines J Hepatol 2012
Early and very early stages 2 – percutaneous treatment

• Small tumor, BCLC 0 – A, not suitable for surgery
• Radiofrequency Tumor Ablation
  – > alcohol if >2cm,
  – Less session, more side effects (NS), more expensive;
• Chemical destruction (alcohol, acetic acid)
  – < 3 cm; 5 years OS: 40–50%,
  – If RFA not technically feasible;
• Microwaves, cryotherapy: under investigation
• Currently: extension of RFA
  – 2 – 3 tumors ¹, up to 5 cm ² or larger³?
  – RFTA + PEI ⁴?
• No adjuvant treatment.

Treatment of intermediate-stage hepatocellular carcinoma

Alejandro Forner, Marine Gilabert, Jordi Bruix and Jean-Luc Raoul


Key points

- A number of treatments are available for hepatocellular carcinoma (HCC), and their allocation—as well as disease prognosis—is influenced by tumour stage and the degree of liver-function impairment.
- The current definition of intermediate-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage B) is extensive multifocal disease confined to the liver, with preserved liver function and no cancer-related symptoms.
- Transarterial chemoembolization (TACE) is considered the standard treatment for intermediate-stage HCC in patients with preserved liver function and no cancer-related symptoms.
- Major efforts have been made to improve outcomes among patients treated with TACE; accurate technique together with appropriate patient selection is key to obtaining the best results.
- Sorafenib, the only systemic treatment associated with a survival benefit in HCC, should be considered for patients with BCLC stage B HCC who are not eligible for TACE.
- Radioembolization has antitumoural efficacy in patients with intermediate-stage HCC, but evidence of survival benefit has not been presented and is awaited.
Intermediate stage
Loco-regional treatments

- Different loco-regional treatments: TACE, RE, TAE, XRT
- RE, XRT: promising, investigational
- TAE: not recommended
- TACE:
  - Results based on one meta-analysis \(^1\)
  - Another one was negative \(^2\)
  - cTACE = DEB-TACE \(^3\):

1. Llovet JM, Bruix J. Hepatology 2003; 37: 429-42
Indication

- Treatment of intermediate-stage (BCLC B) HCC

  - Decompensated cirrhosis (Child–Pugh B ≥8) including:
    - Jaundice
    - Clinical encephalopathy
    - Refractory ascites
    - Hepatorenal syndrome
  - Extensive tumour with massive replacement of both entire lobes
  - Severely reduced portal vein flow (e.g. non-tumoural portal vein occlusion or hepatofugal blood flow)
  - Technical contraindications to hepatic intra-arterial treatment, e.g.

- Only patients with good performance status, adequate liver function, and with tumours without vascular invasion or extra-hepatic spread have been shown to benefit from cTACE.

- Comorbidities involving compromised organ function:
  - Active cardiovascular disease\(^a\)
  - Active lung disease\(^b\)
  - Untreated varices at high risk of bleeding
  - Bile-duct occlusion or incompetent papilla due to stent or surgery

\(^a\) Active cardiovascular disease includes those diseases caused by underlying atherosclerosis (e.g. aortic aneurysm, cerebrovascular accident, congestive heart failure, angina pectoris, coronary artery disease, recent myocardial infarction, severe peripheral vascular disease, large aortic or hepatic arterial aneurysm).

\(^b\) Clinically active disease that requires oxygen support or multiple drug treatment.
**cTACE Contra-indications**

**Absolute contraindications**
- Decompensated cirrhosis (Child-Pugh B ≥8) including:
  - Jaundice
  - Clinical encephalopathy
  - Refractory ascites
  - Hepatorenal syndrome
- Extensive tumour with massive replacement of both entire lobes
- Severely reduced portal vein flow (e.g. non-tumoural 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)
Relative contraindications

- Tumour size $\geq 10$ cm
- Comorbidities involving compromised organ function:
  - Active cardiovascular disease$^a$
  - Active lung disease$^b$
- Untreated varices at high risk of bleeding
- Bile-duct occlusion or incompetent papilla due to stent or surgery
cTACE

How to appreciate efficacy?

• Imaging:
  – Intratumoral retention of Lipiodol: intense & complete
    • Considered as CR for some authors?
    • On resected specimen: ypCR in 56%\(^1\)
    • But: better prognostic.
  – Size: unidimensional RECIST or WHO: YES, but not so good…

• Contrast enhanced imaging: \(^2, 3, 4\)
  – EASL or mRECIST (bi or unidimensional): « viable » part
  – Better predictive value of prognostic than RECIST or WHO

• AFP:
  – Some value;
  – Particularly if: very high => major decrease \(^4\)

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How to manage treatment

Untreatable progression:
- In pretreated area;
- Major progression;
- Contra-indications:
  - Portal Vein Thombosis
  - Metastases,
  - Worsening of cirrhosis,
  - Poor PS.
How to manage treatment: scores: ART score

<table>
<thead>
<tr>
<th>ART - score</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of radiologic response</td>
<td>1</td>
</tr>
<tr>
<td>AST increase &gt; 25%</td>
<td>4</td>
</tr>
<tr>
<td>Child Pugh score increase 1 point</td>
<td>1,5</td>
</tr>
<tr>
<td>≥ 2 points</td>
<td>3</td>
</tr>
</tbody>
</table>

Just before second TACE session
cTACE

How to manage treatment: scores?

• **ART Score**: ¹
  – Not validated: in Japan², in Italy³,
  – Not validated in France⁴:

• **ABCR Score**: same methodology
  – Score:  
    - AFP (/200): 0, 1 - BCLC: 0, 2, 3
    - Child: 0, 0, 2 - Response: 0, -3

Terzi E, et al. Dig Dis 2014;
cTACE
TACE + antiangiogenic drugs

- Randomized Phase II: TACE + sorafenib (154) vs. + placebo (153)

The BCLC staging system is recommended for prognostic selection and treatment assignment.

HCC:

- Very early stage (0)
  - Single <2cm
  - Child-Pugh A, PS 0
  - Potential candidate for liver transplantation

- Early stage (A)
  - Single or ≤3 nodules <3cm
  - Child-Pugh A–B, PS 0
  - Single
  - Portal pressure
  - Bilirubin

  - Yes: 
    - ≤3 nodules
    - Associated diseases
    - Yes: Ablation
    - No: Resection

  - No: Transplant

- Intermediate stage (B)
  - Large multinodular
  - Child-Pugh A–B, PS 0
  - Ablation

- Advanced stage (C)
  - Portal invasion
  - Extrahepatic spread
  - Child-Pugh A–B, PS 1–2
  - TACE
  - Sorafenib

- Terminal stage (D)
  - Child-Pugh C, PS 3–4
  - BSC

Curative treatments:
- Ablation
- Resection
- Transplant
- Ablation

Palliative treatments:
- TACE
- Sorafenib
- BSC

Advanced stages: Systemic treatments: Sorafenib

Sorafenib
Median: 10.7 mo
95% CI: 9.4-13.3

Placebo
Median: 7.9 mo
95% CI: 6.8-9.1

HR (95% CI): 0.69 (0.55-0.87)
P < 0.001

Post-TACE:

HR (95% CI): 0.58 (0.45-0.74)
P < 0.001

Bruix J, et al J Hepatol 2012;
Systemic treatments: Sorafenib: indications

- **Advanced stage:**
  - Portal vein invasion,
  - Extra-hepatic metastases,
  - Child-Pugh A, B
  - PS: 0 – 2

- **SHARP trial:**
  - Advanced stages BCLC or progression after TACE
  - PS 0, 1, 2
  - Child-Pugh A
  - Biology « correct »

- **No clinical or molecular biomarker available.**
Sorafenib: How to assess efficacy?

- Survival benefit without response;
- Response rate: 2 - 3%, stabilisation 55 – 70% WHO– RECIST
- Ce Imaging based criteria:
  - mRECIST: unidimensional
  - EASL: bidimensional
  - In WHO, pay attention to:
    - Ascites or pleural effusion: cytology
    - Node: >20 mm or hypervascularized
    - New lesions: wash-in/wash out and > 10 mm
    - Portal Vein Thrombosis: if hypervascularized

Edeline J, et al Cancer 2012  
Rondo M, et al Oncologist 2014  
Reig M, et al Semin Liver Dis 2014  
Lencioni R, et al J Hepatol 2017
• **SHARP trial:**
  – Unacceptable Toxicity,
  – Radiological and Symptomatic Progression

• **In « real life »:**
  – Radiological and Symptomatic Progression
  but
  – Symptomatic Progression # toxicity ?
  – Radiological Progression?: ce Criteria (mRECIST, EASL)

Sorafenib:?

Stopping rules: pattern of progression

Tumor PD but: good PS, good liver function (Child-Pugh A)

Second line after sorafenib: regorafenib: RESORCE trial

- **RESORCE trial:**
  - Progression during sorafenib
  - In patients who tolerated well sorafenib (> 400 mg/d, 20 d/month)

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS*</td>
<td>10.6 m</td>
<td>7.8 m</td>
</tr>
<tr>
<td>mTTP*</td>
<td>3.2 m</td>
<td>1.5 m</td>
</tr>
<tr>
<td>ORR*</td>
<td>10.6%</td>
<td>4.1%</td>
</tr>
<tr>
<td>DCR*</td>
<td>65.2%</td>
<td>36.1%</td>
</tr>
</tbody>
</table>

**Table of survival outcomes:**

- **HR:** 0.63 (95% CI 0.50-0.79), one-sided p < 0.001

**Graph:**

- Probability of survival (%) over time
- Regorafenib vs Placebo

**Reference:**

Immunotherapy
Highly promising!

Nivolumab:

Figure 1. CheckMate 040 Study Design

- **Dose Escalation**
  - 0.1–10 mg/kg
  - N = 48
  - Uninfected (n = 23)
  - HCV infected (n = 10)
  - HBV infected (n = 15)

- **Dose Expansion**
  - 3 mg/kg
  - N = 214
  - Uninfected (n = 113)
  - HCV infected (n = 50)
  - HBV infected (n = 51)

- **Sorafenib**
  - Experienced (2L) (n = 37)
  - Naive (1L) (n = 11)

- **Study Endpoints**
  - **Primary**
    - Safety and tolerability (escalation)
    - Objective response rate (expansion)
  - **Secondary**
    - Objective response rate (escalation)
    - Disease control rate
    - Time to response
    - Duration of response
    - Overall survival
  - **Other**
    - Biomarker assessments
    - Patient-reported outcomes

- Interim analysis data cutoff date: August 8, 2016
- Median follow-up was 13.3 months in the dose-escalation phase and 10.5 months in the dose-expansion phase

Mellero I et al. ASCO GI 2017
**Immunotherapy**
Highly promising!

**Nivolumab:**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Investigator Assessment</th>
<th>BICR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose Escalation (n = 37)</td>
<td>Dose Expansion (n = 145)</td>
</tr>
<tr>
<td>Objective response by RECIST v1.1</td>
<td>6 (16.2)</td>
<td>27 (18.6)</td>
</tr>
<tr>
<td>Complete response</td>
<td>3 (8.1)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (8.1)</td>
<td>24 (16.6)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>16 (43.2)</td>
<td>66 (45.5)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (32.4)</td>
<td>46 (31.7)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (8.1)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Objective response by mRECIST</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BICR, blinded-independent central review.
Late stage
Symptomatic treatments: Best Supportive Care

• Sleep disturbances:
  – Sleep and hygiene practices
  – Treat encephalopathy? Hydroxizyme 25 mg

• Depression, anxiety:
  – Diet, exercise, hygiene
  – Selective Serotonin Reuptake Inhibitors (SSRI): safest class;

• Fatigue: exercise

• Anorexia, sarcopenia, malnutrition
  – Frequent meals (6-7/d), one evening meal
  – Oral nutritional supplement: 800 – 1000 cal/d, nasoenteric tube
  – Branched Chain Amino Acids.
Late stage
Symptomatic treatments: Best Supportive Care

• Pain:
  – Paracetamol: up to 2.4 g/d
  – No NSAIDs

• Morphine:
  – Hydromorphone and fentanyl: may be the better choice,
  – Initially: lower dose - longer interval - good titration: 2 – 3 days,
  – Assessment of efficacy / tolerance on a regular basis,
  – Titration with short active opioids,
  – When pain is controlled:
    • Use long-acting agents (q12h or q3d)
    • And if necessary short active drug (1/6 – 1/7th)
    • Dose adaptation (+ 20-30%) if / when necessary

• In association with paracetamol
To conclude

• Some progress
• Importance of the BCLC
• I can do it, different from: it is of value for the patient
• Many lines: strategies!
TACE

Overall survival

Child A-B7, PS 0

TACE

TACE

TACE

TACE

B S C

Sorafenib

B S C

Sorafenib

B S C

Sorafenib

Rego

Overall survival
Child A-B7, PS 0

TACE

TACE

TACE

Overall Survival

TACE

TACE

Sorafenib

Sorafenib

Sorafenib

Rego
Thank you!