Diagnosis of HCC
Diagnosis of HCC

- HCC in HIV+
- Risk factors for HCC
- Screening for HCC
- Diagnosis of HCC
- Staging HCC
Diagnosis of HCC

- HCC in HIV+
- Risk factors for HCC
- Screening for HCC
- Diagnosis of HCC
- Staging HCC
Hepatocellular Carcinoma

• Hepatocellular carcinoma (HCC) is a primary malignancy of the liver.
• It is now the third leading cause of cancer deaths worldwide, with over 500,000 people affected.
• Hepatitis and excessive alcohol are the leading causes of HCC.
• With cirrhosis in about 80%
Compensated cirrhosis: absence of jaundice, ascites, portal-systemic encephalopathy or variceal bleeding

Standardized incidence ratios (SIRs) for non–AIDS-defining malignancies

### Table

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Meta-analysis SIR (95% CI)</th>
<th>Studies, n</th>
<th>Observed number of cancers</th>
<th>Heterogeneity P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>0.70 (0.55–0.89)</td>
<td>6</td>
<td>202</td>
<td>0.22</td>
</tr>
<tr>
<td>Trachea, bronchus and lung</td>
<td>2.72 (1.91–3.87)</td>
<td>7</td>
<td>1016</td>
<td>0.00</td>
</tr>
<tr>
<td>HCC</td>
<td>5.22 (3.32–8.20)</td>
<td>7</td>
<td>133</td>
<td>0.01</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>0.92 (0.78–1.08)</td>
<td>5</td>
<td>224</td>
<td>0.34</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>5.82 (2.98–11.2)</td>
<td>6</td>
<td>104</td>
<td>0.00</td>
</tr>
<tr>
<td>Breast</td>
<td>1.03 (0.89–1.20)</td>
<td>6</td>
<td>194</td>
<td>0.60</td>
</tr>
<tr>
<td>Anal</td>
<td>28.75 (21.6–38.3)</td>
<td>6</td>
<td>303</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Log-SIRs for non–AIDS-defining malignancies with available screening interventions
Hepatocarcinogenesis is a multi-step process

Increased prevalence in HIV+

HBV
HCV
Alcohol
AFB1
Genetic disease
Male
Gender
Diabetes
Obesity

HBV, HCV, Alcohol, AFB1, Genetic disease, Male Gender, Diabetes, Obesity

HBV
HCV
Alcohol
AFB1
Genetic disease
Male
Gender
Diabetes
Obesity

Hepatocarcinogenesis is a multi-step process involving various factors such as HBV, HCV, Alcohol, AFB1, Genetic disease, Male Gender, Diabetes, and Obesity. The process includes chronic hepatitis, cirrhosis, and genetic and epigenetic alterations, which can lead to dysplastic hepatocytes and ultimately hepatocellular carcinoma (HCC). The diagram illustrates the progression from preneoplasia (10 to 30 years) to dysplasia (3 to 5 years) and neoplasia (< 5 years). Genetic and epigenetic alterations play a crucial role in this process, including mutations such as p53, β-catenin, and Axin.
Diagnosis of HCC

• HCC is more common in HIV+ than in general population because of higher prevalence of risk factors:
  – Viruses (HBV, HCV, HD)
  – Alcohol abuse
  – NASH
  – Faster progression of liver diseases towards cirrhosis
Hepatocellular carcinoma-related deaths in 2000 (N = 16) and in 2005 (N = 35) according to hepatitis co-infections Mortalité 2000 and Mortalité 2005 surveys, France
Trends in the prevalence of cirrhosis, decompensated cirrhosis, HCC and mortality in 24,040 HIV–infected veterans during period 1996-06 presented according to HCV status.
HCC

• HCC is more common in HIV+ than in general population because of higher prevalence of risk factors

• HCC is an increasing cause of death in HIV+ in developed countries
Diagnosis of HCC

• HCC in HIV+
• Risk factors for HCC
• Screening for HCC
• Diagnosis of HCC
• Staging HCC
Insulin resistance is associated with a higher risk of hepatocellular carcinoma in cirrhotic HIV/HCV-co-infected patients: Results from ANRS CO13 HEPAVIH

- 244 HIV/HCV with cirrhosis (clinically or histologically proven cirrhosis or Liver Stiffness ≥ 12.5 KPa)
- 21 (8.6%) developed HCC during a mean follow up of 2.6 years (95% CI 1.8-3.5)
- Predictors of HCC by multivariate analysis:
  - Age > 50 yrs (ARR 3.2 95% CI 1.2-9) p=0.02
  - HOMA > 3.8 (ARR 3.4 95% CI 1.1-10.3) p = 0.03

Salmon D et al. J Hepatol 2012; 56 : 862-68
Does HIV increase the risk for HBV-induced HCC?

• South African case-control study in pre-HAART era (Kew et al JAIDS 2010; 53:413)
  – Prevalence of HIV infection in 6/178 (3.4%) with HBV-induced HCC compared to 0/185 age- and sex-matched HBV carriers ($P = 0.036$)

• Swiss HIV cohort case-control (1:10) study suggests HIV-related immunosuppression increases HCC risk in MSM with high HBV prevalence

<table>
<thead>
<tr>
<th></th>
<th>IDU</th>
<th>MSM/heterosexual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCC N=14</td>
<td>Controls N=122</td>
</tr>
<tr>
<td>HBsAg+, %</td>
<td>28.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Anti-HCV+, %</td>
<td>92.9</td>
<td>90.9</td>
</tr>
<tr>
<td>Per 100 cell/uL ↓ in latest CD4</td>
<td>1.13 (0.86-1.48)</td>
<td>1.68 (1.15-2.46)</td>
</tr>
</tbody>
</table>

REVEAL.: High HBV viral load is associated with increased incidence of HCC

Cumulative incidence of HCC: All subjects (n=3,653)

Baseline HBV DNA Level, copies/mL
- ≥10^6
- 10^5–<10^6
- 10^4–<10^5
- 300–<10^4
- <300

Seroclearance of HBVDNA predicts significantly reduced risk of HCC among those with high viral loads: a time dependent analysis of serially measured biomarkers

REVEAL 3000 non cirrhotics (30-65 yrs) 7 township Taiwan 1991. Screening every 6/12 mo. 153 HCCs. Antiviral therapy?

<table>
<thead>
<tr>
<th>MAHR for HCC</th>
<th>All (2946)</th>
<th>HBVDNA detectable (n=2191)</th>
<th>HBeAg seropositive (N 444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg seroclearance: Yes vs no</td>
<td>0.63 (0.29-1.38)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>HBVDNA decreased to undetectable Yes vs no</td>
<td>0.37 (0.16-0.86)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>HBeAg seroclearance Yes vs no</td>
<td>0.97 (0.56-1.69)</td>
<td>0.92</td>
<td></td>
</tr>
</tbody>
</table>

*Also adjusted for age, gender, smoking, alcohol consumption, ALT levels, § HBeAg serostatus and ° HBVDNA levels

Liu J et al EASL 2013 Abstract # 40
## Risk scores for HBV related HCC

<table>
<thead>
<tr>
<th>Score</th>
<th>Patients</th>
<th>Components</th>
<th>Cut-off</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CU-HCC¹</td>
<td>Clinic: 1005 in training cohort 424 in validation cohort</td>
<td>Age, albumin, bilirubin HBVDNA, cirrhosis</td>
<td>5</td>
<td>97% NPV at 5 years</td>
</tr>
<tr>
<td>GAG-HCC²</td>
<td>820 clinic patients (leave-one-out-cross validation method)</td>
<td>Age, gender, HBVDNA, cirrhosis</td>
<td>101</td>
<td>99% NPV at 10 years</td>
</tr>
<tr>
<td>REACH-B³</td>
<td>Non cirrhotic patients: 3584 in training cohort 1505 in validation cohort</td>
<td>Age, gender, ALT, HBVDNA, HBeAg</td>
<td>8</td>
<td>98% NPV at 10 years</td>
</tr>
</tbody>
</table>

1. Wong VW et al J Clin Oncol 2010;
2. Yuen MF et al J Hepatol 2009;
# Performance of HCC risk scores in chronic hepatitis B patients receiving entecavir

<table>
<thead>
<tr>
<th></th>
<th>CU HCC</th>
<th>GAG-HCC</th>
<th>REACH- B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cut Offs</td>
<td>5</td>
<td>101</td>
<td>8</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94%</td>
<td>55%</td>
<td>95%</td>
</tr>
<tr>
<td>Specificity</td>
<td>48%</td>
<td>79%</td>
<td>17%</td>
</tr>
<tr>
<td>PPV</td>
<td>5%</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>YEAR 2 ON TREATMENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>86%</td>
<td>68%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>56%</td>
<td>88%</td>
<td>53%</td>
</tr>
<tr>
<td>PPV</td>
<td>3%</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>99%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Wong VW EASL 2013 abstract # 44
### Long term Tenofovir Disoproxil Fumarate therapy and the risk of HCC (REACH-B)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cirrhotic (=152)</th>
<th>Non cirrhotic (n=482)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age years (SD)</td>
<td>45.2 (10.6)</td>
<td>38.4 (11.8)</td>
</tr>
<tr>
<td>Male n. (%)</td>
<td>123 (81)</td>
<td>345 (72)</td>
</tr>
<tr>
<td>Race n. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White n(%)</td>
<td>92 (61)</td>
<td>283 (59)</td>
</tr>
<tr>
<td>Asian n (%)</td>
<td>39 (26)</td>
<td>148 (31)</td>
</tr>
<tr>
<td>Other n (%)</td>
<td>21 (13)</td>
<td>51 (10)</td>
</tr>
<tr>
<td>HBeAg positive n (%)</td>
<td>60 (40)</td>
<td>283 (59)</td>
</tr>
<tr>
<td>Mean HBVDNA log10 copies/mL</td>
<td>7.6 (1.4)</td>
<td>7.7 (1.5)</td>
</tr>
<tr>
<td>Mean ALT U/L (SD)</td>
<td>143.2 (123.4)</td>
<td>143 (113.1)</td>
</tr>
<tr>
<td>HBV Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>34 (23)</td>
<td>67 (14)</td>
</tr>
<tr>
<td>B</td>
<td>10 (7)</td>
<td>64 (14)</td>
</tr>
<tr>
<td>C</td>
<td>27 (18)</td>
<td>83 (18)</td>
</tr>
<tr>
<td>D</td>
<td>73 (49)</td>
<td>239 (51)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3)</td>
<td>20 (4)</td>
</tr>
</tbody>
</table>

Kim WR et al EASL 2013 Abstract # 43
Long term Tenofovir Disoproxil Fumarate therapy and the risk of HCC (REACH-B)

Observed vs predicted HCC cases:
Non cirrhotics
Effect of TDF noticeable at 2 years of therapy and became significant at 6 years 55%

Observed vs predicted HCC cases:
Cirrhotics
Statistically significant at nominal $\alpha$ level of 0.05
Ci: Confidence Interval, SIR Standard Incidence Ratio

Kim WR et al EASL 2013 Abstract # 43
<table>
<thead>
<tr>
<th>Authors</th>
<th>Abstract</th>
<th>Patients</th>
<th>Cirrhotics</th>
<th>Fup (mo)</th>
<th>HCC yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lampertico</td>
<td>755</td>
<td>418</td>
<td>155</td>
<td>52 (2-66)</td>
<td>2.8%</td>
</tr>
<tr>
<td>Papatheodoridis</td>
<td>766</td>
<td>321</td>
<td>69</td>
<td>30+18</td>
<td>2.6%</td>
</tr>
<tr>
<td>Chen §</td>
<td>521</td>
<td>706/196</td>
<td>706/196</td>
<td>36+19</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

HCC risk in HBeAg negative patients on long term entecavir: EASL 2013
Diagnosis of HCC

- HCC in HIV+
- Risk factors for HCC
- Screening for HCC
- Diagnosis of HCC
- Staging HCC
Primary liver cancer is more aggressive in HIV-HCV coinfection than in HCV infection.

A prospective study (ANRS CO13 Hepavih and CO12 Cirvir)

- Two prospective cohorts (ANRS CO12 Cirvir, viral cirrhosis, \( n = 1081 \); ANRS CO13 Hepavih, HIV-HCV coinfection, \( n = 1175 \))
- 32 cases of HCC (16+16)

<table>
<thead>
<tr>
<th>Character</th>
<th>HIV+</th>
<th>HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since last US FUP days</td>
<td>237</td>
<td>208</td>
</tr>
<tr>
<td>Age mean yrs</td>
<td>48</td>
<td>60*</td>
</tr>
<tr>
<td>Single nodule</td>
<td>43%</td>
<td>75%°</td>
</tr>
<tr>
<td>Mean diameter of main nodule mm</td>
<td>24</td>
<td>16*</td>
</tr>
<tr>
<td>Portal obstruction</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Curative Tx</td>
<td>4</td>
<td>11 §</td>
</tr>
<tr>
<td>Death at fup</td>
<td>10</td>
<td>1*</td>
</tr>
</tbody>
</table>

* \( p < 0.01 \); § \( p < 0.05 \); ° \( p = 0.07 \)

### Surveillance for HCC

**Table 3. Recommendations for HCC surveillance: categories of adult patients in whom surveillance is recommended.**

<table>
<thead>
<tr>
<th></th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cirrhotic patients, Child-Pugh stage A and B*</td>
</tr>
<tr>
<td>2</td>
<td>Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation**</td>
</tr>
<tr>
<td>3</td>
<td>Non-cirrhotic HBV carriers with active hepatitis or family history of HCC***</td>
</tr>
<tr>
<td>4</td>
<td>Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3****</td>
</tr>
</tbody>
</table>

*Evidence 3A; strength B1;**  
**evidence 3D; strength B1;  
***evidence 1B; strength A1 for Asian patients; evidence 3D; strength C1 for Western patients;  
****evidence 3D; strength B1 for Asian patients; evidence 3D; strength B2 for Western patients.
CANDIDATES

- **Cirrhotic patients, Child-Pugh class A and B** (evidence 2b, strength B)

- **Cirrhotic patients, Child-Pugh class C awaiting liver transplantation** (evidence 5, strength D)

- **Non cirrhotic patients with chronic hepatitis B or inactive hepatitis B carriers with viremia >2000 UI/ml**
  (evidence 3b, strength B for Western patients; evidence 1b, strength A for Oriental patients)

- **Non cirrhotic patients with chronic hepatitis C and liver fibrosis ≥F3 Metavir (o ≥10 Kpa at transient elastography [Fibroscan®])**
  (evidence 5, strength D for Western patients; evidence 3b, strength B for Oriental patients)

- **Patients with chronic HCV and HBV hepatitis successfully treated (negative viremia), but corresponding to any of the previous at risk categories prior to starting antiviral treatment** (evidence 5, strength D)

  Surveillance is recommended for the above patients if they do not have contraindications to radical or palliative treatments.
FIB-4 index is associated with Hepato Cellular Carcinoma risk in HIV-infected patients.

- 2,980 HIV-infected men from the Veterans Aging Cohort Study
- 112 HCC incident diagnoses

<table>
<thead>
<tr>
<th>FIB 4</th>
<th>Unadjusted HR* (95% Confidence Interval)</th>
<th>Multivariate Adjusted HR** (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (&lt;1.45 )</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.2 (2.4-7.4)</td>
<td>3.6 (2.1-6.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (7.2-23.4)</td>
<td>9.6 (1.2-17.4)</td>
</tr>
</tbody>
</table>

*Adjusted for age- and race/ethnic group

** Adjusted for enrollment year, CD4 count, HIV-1 RNA level, antiretroviral therapy use, hepatitis B and C virus infection, alcohol abuse/dependency, and diabetes

Algorithm for the identification of patients with cirrhosis
Istituto di Malattie Infettive Università di Brescia

<table>
<thead>
<tr>
<th>INDEX</th>
<th>PARAMETER</th>
<th>Formula</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIB4</td>
<td>PLT, AST, ALT, ETA'</td>
<td>(ETA' x AST)/(PLT x ALT^1/2)</td>
<td>&lt;1.45 = METAVIR &lt;3-4; &gt;3.25 = METAVIR &gt;3-4</td>
</tr>
</tbody>
</table>

352 HCV+ → FIB4

- FIB 4: < 1.45 → 165 → Non cirrhotic 160 VN 5 FN
- FIB 4: 1.45 - 3.25 → FIBROSCAN 
  - Stiffness > 13: 82 Cirrosi 76 VP 6 FP
  - Stiffness < 13: 13 Biopsia
- FIB4 > 3.25: 95
  - FIBROSCAN
    - Stiffness > 10: 90 Cirrosi 84 VP 6 FP
    - Stiffness < 10: 5
      - Biopsia

Biopsia epatica casi 18 (5%)
Brescia HCC Screening Pilot study

Enrolment: 01/01/2002 → 01/04/2008
End of FU Dec 1st 2008
158 pts → 2 HCC at diagnosis
156 pts followed up for 412 pp/yy
Median follow up: 30 mo (IQR 13-50 mo)
19 cases of HCC (13%): 4,6 per 100 pp/yy (95% CI 2,6-6,6)

6 patients OLT all 6 locoregional therapy or TACE before OLT
4 resection
4 locoregional Tx
5 untreated at Dx (stage C-D BCLC classification) (26%)
Overall Survival:
1 yr 71% (95% CI 44-87%)
3 and 5 yrs 41% (95% CI 14-65%)

Other series of HCC in HIV:
63 cases US and Canada: survival 22% at 1 yr Untreatable at Dx 52% Brau N et al J Hepatology 2007
41 cases Italy and Spain: survival 28% at 1 year and 11% at two years. Untreatable at dx 60% Puoti M et al. AIDS 2004
Screening for Hepatocellular Carcinoma (HCC) in HIV/HCV-Coinfected Patients: Impact on Survival

At Risk
HCC Screen 39 10 5 3 1
No HCC Screen 31 0

Actuarial median survival:
HCC screen 12.8 months
No HCC screen 3.7 months

Brau N et al. CROI 2010
HCC: Screening

- Identification of pts with cirrhosis is feasible even in large cohorts of HIV+
- US screening of HIV infected patients with diagnosis of or suspected to have cirrhosis seems to be useful to:
  - identify predictors of HCC which could select patients candidates for more proactive recall screening strategies
  - obtain an earlier diagnosis of HCC → higher proportion of treatable cases

Impact on patients’ survival should be assessed in case control studies
Diagnosis of HCC

- HCC in HIV+
- Risk factors for HCC
- Screening for HCC
- Diagnosis of HCC
- Staging HCC
**HCC radiological hallmark: arterial hypervascularity and venous/late phase washout**

* One imaging technique only recommended in centers of excellence with high-end radiological equipment.

Diagnostic Recall policy: Italian perspective

New lesion in cirrhosis

- **∅ < 1 cm**
  - US/3 mo
  - Yes: Increase (∅ > 1 cm)
  - No: US/3 mo (for 12 mo)
  - Yes: increase (∅ > 1 cm)
  - No: US /6 mo

- **∅ > 1 cm**
  - TC, RM, CEUS
  - Hallmarks (wash-in & wash-out)
  - No:
    - No Hallmarks
    - Hallmarks
  - Yes: Biopsy

Other diagnosis

No Diagnosis

HCC

Raccomandazioni AISF per la gestione integrata del paziente con Epatocarcinoma; published on www.webaisf.org
Small resectable HCC in a 47-year-old woman. (a, b) Contrast-enhanced arterial phase CT images in the axial (a) and coronal (b) planes show an exophytic HCC (arrow) that involves the lateral segment of the left hepatic lobe. (c) Photograph shows the HCC-containing liver specimen that was excised by using a laparoscopic hand-assisted left lateral wedge resection.
Diagnosis of HCC

- HCC in HIV+
- Risk factors for HCC
- Screening for HCC
- Diagnosis of HCC
- Staging HCC
HCC staging is multifaceted

- Staging is used for prognosis and to guide treatment\(^1\)

- Staging HCC\(^1\)
  - 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\(^2,3\)
  - tumour stage
  - liver function
  - health status
  - efficacy of treatment

ECOG PS = Eastern Cooperative Oncology Group Performance Status; TNM = tumour–node–metastases

---

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

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

End stage (D)
PST > 2, Child–Pugh C

Resection
Liver transplantation
PEI/RFA

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

TACE
Sorafenib
Best supportive care

Target: 20%
Target: 40%
Target: 10%

OS: 20 mo (45-14)
OS: 11 mo (6-14)
OS: <3 mo

Portal pressure/bilirubin
Increased
Normal

3 nodules ≤ 3 cm

Associated diseases
No
Yes

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
- Rafs/Raf/MAPKs
- Hippo (YAP, Mst1/2, Lats1/2)

**INFLAMMATION**
- IFN
- IL6
- JAK / STATs

**ANGIOGENESIS**
- VEGF
- FGF
- PDGF

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

**NUCLEAR EFFECTORS**
- NFκB
- STATs
- Gli 1 / 2
- HIF-1α

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

**miRNAs**
<table>
<thead>
<tr>
<th>Stage</th>
<th>VERY EARLY / EARLY STAGE (BCLC-0/A)</th>
<th>INTERMEDIATE STAGE (BCLC-B)</th>
<th>ADVANCED STAGE (BCLC-C)</th>
<th>TERMINAL STAGE (BCLC-D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Therapy</td>
<td>Curative treatments</td>
<td>Chemoembolization</td>
<td>Sorafenib</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Predicted Survival</td>
<td>&gt; 60 months</td>
<td>~ 20 months</td>
<td>~ 11 months</td>
<td>&lt; 3 months</td>
</tr>
</tbody>
</table>

**Adjacent Tissue Profiling**

- Genomic risk for de novo tumors
- Genomic risk for intrahepatic metastasis
- Genomic predictors of tumor aggressiveness (e.g., vascular invasion, satellites, poor differentiation)

*Villanueva A et al., Annual Reviews of Medicine, 2010*
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)
A Meta-Analysis of Survival Rates of Untreated Patients in Randomized Clinical Trials of Hepatocellular Carcinoma

Untreated control groups of 30 RCTs

1-year survival rate

17.5%

p for heterogeneity < 0.0001

2-year survival rate

7.3%

Range 0 – 75%

Range 0 – 50%

Untreated control groups of 30 RCTs

Lai (98)
Pelletier (96)
Lee (99)
Madrid (93)
Elba (94)
Cerezo (94)
GRETCH (95)
Monreal (95)
Coste (96)
Grimaldi (96)
Kouroumas (98)
Rostron (98)
Brixi (98)
CLIP Group (98)
Chung (00)
Liew (00)
Liu (00)
Villa (01)
Ishikawa (01)
Lo (02)
Liew (02)
Yuen (02)
Chow (02)
Barbare (95)
Sarin (96)
Becker (97)
Dimidisopoulos (97)
Liew (98)
Cheng (99)
Barbare (99)
Summary

Cabibbo et al. Hepatology 2010
Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome

Massimo Puoti, Raffaele Bruno\textsuperscript{a}, Vincent Soriano\textsuperscript{b}, Francesco Donato\textsuperscript{c}, Giovanni Battista Gaeta\textsuperscript{d}, Gian Paolo Quinzan\textsuperscript{e}, Davide Precone\textsuperscript{f}, Umberto Gelatti\textsuperscript{c}, Victor Asensi\textsuperscript{f} and Emanuela Vaccher\textsuperscript{g} for the HIV HCC Cooperative Italian–Spanish Group*
Comparison between Kaplan Meier survival curves of the 41 anti HIV positive patients with HCC from GICAT registry and: the 384 anti HIV negative patients from Brescia HCC study group database.
Tumour characteristics of 585 pts with HCC: 104 HIV+ vs. 484 HIV-

Tab 2. Tumor characteristics and relative treatment

<table>
<thead>
<tr>
<th></th>
<th>HIV positive (n=104)</th>
<th>HIV negative (n=484)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis under screening program</td>
<td>58 (55.7%)</td>
<td>371 (76.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time from CLD to HCC mean (years)</td>
<td>15.2±3.6</td>
<td>24.5±5.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stage at diagnosis (BCLC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>29 (27.9%)</td>
<td>64 (13.3%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>40 (38.5%)</td>
<td>141 (29.1%)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>C</td>
<td>11 (10.5%)</td>
<td>223 (46.0%)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>24 (23.1%)</td>
<td>56 (11.6%)</td>
<td></td>
</tr>
<tr>
<td>AFP serum levels (ng/ml) [median][range]</td>
<td>420 [1.3-25120]</td>
<td>478 [1.0-7800]</td>
<td>0.716</td>
</tr>
<tr>
<td>Treated after diagnosis (all treatment)</td>
<td>89 (85.6%)</td>
<td>317 (65.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Potentially Curative therapy</td>
<td>40 (44.9%)</td>
<td>162 (51.1%)</td>
<td>0.066</td>
</tr>
<tr>
<td>RFA/PEI</td>
<td>15 (16.8%)</td>
<td>75 (23.6%)</td>
<td></td>
</tr>
<tr>
<td>Surgical Resection</td>
<td>13 (14.7%)</td>
<td>40 (12.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Liver Transplantation</td>
<td>7 (7.8%)</td>
<td>4 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>RFA+TACE</td>
<td>5 (5.6%)</td>
<td>43 (13.6%)</td>
<td></td>
</tr>
<tr>
<td>Effective, non curative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE</td>
<td>38 (42.7%)</td>
<td>145 (45.7%)</td>
<td>0.631</td>
</tr>
<tr>
<td>Unproven efficacy or other therapies</td>
<td>11 (12.4%)</td>
<td>10 (3.1%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>6 (6.7%)</td>
<td>8 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Systemic Chemotherapy</td>
<td>5 (5.7%)</td>
<td>2 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Recurrence after treatment</td>
<td>63 (70.7%)</td>
<td>196 (61.8%)</td>
<td>0.135</td>
</tr>
<tr>
<td>Treatment at recurrence (all treatments)</td>
<td>40 (61.01%)</td>
<td>169 (86.2%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Beretta et al. The Oncologist 2011
Survival for potentially curative treatment in 45 HIV+ vs. 144 HIV- HCC

Beretta et al. The Oncologist 2011
Survival in HCC pts without curative treatment (TACE and/or Chemotherapy and/or biological drugs) in 49 HIV+ and 135 HIV- pts. with HCC

HR = 1.59 (95% CI 0.93-2.73)
$C^2 = 3.612; \ p = .051$ (Log-Rank test)

Beretta et al. The Oncologist 2011
HCC

- HCC is more common in HIV+ than in general population because of higher prevalence of risk factors
- HCC is an increasing cause of death in HIV+ in developed countries
- Early diagnosis is critical in order to treat HCC
- In HIV+ late diagnosis means less treatable cases and lower survival
## HCC: which strategy?

Factors associated with survival in 585 pts with HCC (104 HIV+)

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% C.I.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCLC stage A-B vs. C-D</td>
<td>2.56</td>
<td>2.11-3.71</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor diameter &lt; 3cm</td>
<td>1.77</td>
<td>1.20-4.02</td>
<td>.029</td>
</tr>
<tr>
<td>PVT*</td>
<td>.605</td>
<td>.355-.921</td>
<td>.015</td>
</tr>
<tr>
<td>HCC curative treatment</td>
<td>1.86</td>
<td>1.59-3.85</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HCC diagnosis under screening program</td>
<td>1.56</td>
<td>1.32-3.56</td>
<td>.021</td>
</tr>
<tr>
<td>Recurrence</td>
<td>.710</td>
<td>.431-.851</td>
<td>.021</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>.835</td>
<td>.634-.958</td>
<td>.049</td>
</tr>
</tbody>
</table>

- **Early diagnosis**
- **Aggressive treatment**
- **Screening of pts at risk**
- **Treat recurrence**
- **Treat HIV**

Beretta et al. The Oncologist 2011