Surveillance of hepatocarcinoma in cirrhotic patients

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Natural history of chronic liver disease

Chronic injury
- Viral infection
- Alcohol
- NASH
- Autoimmune disorders
- Cholestatic disorders
- Metabolic diseases

Genetic polymorphisms
- Epigenetic marks
- Cofactors (such as obesity and alcohol)

5-50 years

Liver failure
- Portal hypertension

Normal liver
- Inflammatory damage
- Matrix deposition
- Parenchymal cell death
- Angiogenesis

Early fibrosis
- Disrupted architecture
- Loss of function
- Aberrant hepatocyte regeneration

Cirrhosis

Liver transplant

Hepatocellular carcinoma

Resolution
- Removal of underlying cause
- Anti-fibrotic drug or cell therapy

Regression

Nature Reviews Immunology

Pellicoro A Nature Reviews Immunology 2014
Outline

• Epidemiology
• Etiology of liver disease
• Risk factors
• Surveillance
Cumulative incidence of HCC according to Geography and Etiology of Cirrhosis
Incidence of HCC according to common etiology of cirrhosis

- **HCV:**
  - From 3.7 to 7.1 x 100 person-years.
  - 5-year cumulative incidence 17% EU and USA vs 30% Japan.

- **HBV:**
  - From 2.2 to 4.3 x 100 person-years.
  - 5-year cumulative incidence 10% EU vs 15% Japan.
Patients with compensated HCV cirrhosis achieving SVR by IFN

795 received IFN-based antiviral therapy
434 patients were not treated because of decompensated
572 compensated patients for comorbidity, ineligibility or refusal.

Outcome of patients with compensated cirrhosis due to chronic hepatitis C virus infection who achieved a sustained virological response (SVR). *Including 4 OLTs.
Matched population with SVR vs General population

Observed deaths: 28
Expected deaths: 28.1
SMR: 1.00 (0.72-1.35)

*Patients with compensated HCV cirrhosis achieving SVR by IFN obtain a main benefit levelling their survival curve and risk of HCC incidence to that of the general population.*
HCV eradication induced by DAAs reduces the risk of HCC

• 62,354 patients who initiated antiviral therapy (AT) in the Veterans Affairs (VA) national healthcare system (1/1/1999 to 12/31/2015):
  – 35,871 (58%) IFN-only regimens
  – 4,535 (7.2%) DAAs+IFN regimens
  – 21,948 (35%) DAAs-only regimens

• Retrospective analysis to identify incident cases of HCC.

Ioannou GN J Hep 2017
• 3.271 incident cases of HCC diagnosed at least 180 days after initiation of AT during a mean follow-up of 6.1 years.

• The incidence of HCC was as follows:
  – 3.25 per 100 patient-years in **cirrhosis and treatment failure**
  – 1.97 per 100-patients years in **cirrhosis and SVR**
  – 0.97 per 100-patients years in **non cirrhotic patients and treatment failure**
  – 0.24 per 100-patients years in **non cirrhotic patients and SVR**
HCC risk after sustained virological response

a. **ALL TREATMENTS**: Kaplan-Meier curves of survival free of HCC by cirrhosis and SVR status after antiviral treatment.

Kaplan-Meier curves of survival free of HCC by cirrhosis and SVR status after DAA-only antiviral treatment: SVR is associated with a reduction in HCC risk both among patients with cirrhosis and those without cirrhosis.

IFN and DAAs

DAAs

Ioannou GN J Hep 2017
Figure 1. Cumulative Incidence of Hepatocellular Carcinoma during Follow-up among 11,893 Men in Taiwan, According to the Presence or Absence of Hepatitis B Surface Antigen (HBsAg) and Hepatitis B e Antigen (HBeAg) at Enrollment. The cumulative incidence was estimated with the use of the Nelson–Aalen method.
Incidence of HCC according to common etiology of cirrhosis

• Alcohol-related:
  – 1.7 x 100 person-years.
  – With viral hepatitis in sharp decline in EU, excessive alcohol consumption will become the main cause of HCC.

Fattovich G Gastroenterology 2004

Alcohol and Digestive Cancers Across Europe: Time fo Change UEG EU affairs 2017
Incidence of HCC according to less common etiology of cirrhosis

- Hereditary hemochromatosis (HH):
  - 5-year cumulative incidence 21%.
HCC and hemochromatosis

• HH patients with cirrhosis have a 100-fold greater chance of developing HCC than the normal population.

• Despite some case reports of HCC in non-cirrhotic patients, screening for HCC is not considered necessary in this group.

EASL Guidelines 2010
Niederau C Gastroenterology 1996
Incidence of HCC according to less common etiology of cirrhosis

- **Primary biliary cholangitis (stage III-IV):**
  - From 0.8 to 1.8 x 100 person-years
  - 5-year cumulative incidence 4%

- **Primary sclerosing cholangitis:**
  - Few data are available (CCA or Hepato-CCA)

- **Autoimmune hepatitis:**
  - 8 (4%) cirrhotic patients developed HCC in a cohort of 217 patients with AIH but 6 of these 8 had evidence of HCV infections

*Fattovich G* Gastroenterology 2004
Incidence of HCC according to less common etiology of cirrhosis

• Wilson’s disease:
  – 2/363 (0.5%) cirrhotic patients 31 and 38 years after diagnosis

• $\alpha_1$-Antitrypsin deficiency:
  – None of 130 patients with $\alpha_1$-ATD deficiency but without chronic liver disease developed HCC in one study
Trajectories in Waiting List Registration over time: 1.117 cases

Padua University Hospital

Delisting HCV after DAAs: 0% to 5.6%

Ferrarese, Transplantation submitted 2017
Trajectories in Waiting List Registration over time: 1.117 cases

Padua University Hospital

*Delisting HCV after DAAs: 0% to 5.6%
NAFLD/NASH and risk of HCC

Cirrhosis Patients with Nonalcoholic Steatohepatitis Are Significantly Less Likely to Receive Surveillance for Hepatocellular Carcinoma

Hesam Tavakoli¹ · Ann Robinson¹ · Benny Liu² · Taft Bhuket² · Zobair Younossi³ · Sammy Saab⁴ · Aijaz Ahmed⁵ · Robert J. Wong²
To evaluate disparities in receipt of routine HCC surveillance among patients with cirrhosis in a large urban hospital.
Risk factors for HCC development

- Older age
- Male gender
- Metabolic syndrome
- Iron overload
- Severity of underlying cirrhosis
Genetic risk markers in alcohol-related HCC

- Ethanol metabolism
- Oxidative stress
- Inflammation process
- Iron or lipid metabolism
Genetic risk markers in alcohol-related HCC

- Ethanol metabolism
- Oxidative stress
- Inflammation process
- Iron or lipid metabolism

Combining genetic information with epidemiological and clinical data might define specific HCC risk classes.
## Table 4. Variables With Independent Predictive Value for HCC in the Multivariate Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>Coefficients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin activity ≤75%</td>
<td>5.21 (1.8-14.9)</td>
<td>1.65</td>
<td>.002</td>
</tr>
<tr>
<td>Age 55 years or older</td>
<td>4.09 (1.8-9)</td>
<td>1.41</td>
<td>.005</td>
</tr>
<tr>
<td>Platelets &lt;75 × 10^3/mm^3</td>
<td>2.5 (1.3-4.9)</td>
<td>0.92</td>
<td>.007</td>
</tr>
<tr>
<td>Presence of anti-HCV antibodies</td>
<td>2.09 (1.1-4.2)</td>
<td>0.74</td>
<td>.03</td>
</tr>
</tbody>
</table>
Cumulative risk according to risk group

4-year cumulative incidence of HCC=30.1%

4-year cumulative incidence of HCC=2.3%

Fig. 1. Cumulative risk (Kaplan-Meier plot) of HCC defined by the score of the 463 patients: low-risk group (4-year cumulative incidence of HCC, 2.3%), high-risk group (4-year cumulative incidence of HCC, 30.1%), and overall estimate of HCC in the 463 patients (Kaplan-Meier estimate).
Surveillance

Surveillance programmes for HCC in cirrhotic patients intend to diagnose the tumour in its early stages when an effective therapy can be applied.
1. EASL-EORTC Practice Guidelines 2012
2. KLCSPG-NCC Korea Practice Guidelines 2014
3. AIOM Guidelines 2015
4. Canadian Gastroenterological Association CASL
5. JSH-HCC Japanese guidelines
6. AISF Guidelines

Italian Multisociety Guidelines HCC 2016
CLINICAL STUDIES

Usefulness of surveillance programmes for early diagnosis of hepatocellular carcinoma in clinical practice

Sonia Pascual¹, Javier Irurzun¹, Pedro Zapater², José Such¹, Laura Sempere¹, Fernando Carnicer¹, Jose María Palazón¹, Pedro de la Iglesia³, Santiago Gil³, Francisco de España³ and Miguel Perez-Mateo¹

¹ Liver Unit, Hospital General Universitario de Alicante, Alicante, Spain
² Clinical Pharmacology Unit, Hospital General Universitario de Alicante, Alicante, Spain
³ Interventional and Vascular Radiological Unit, Hospital General Universitario de Alicante, Alicante, Spain
Survveillance vs non surveillance

Fig. 1. Cumulative survival of each of the two groups of patients with hepatocellular carcinoma using the Kaplan–Meier analysis. SP, surveillance programme; NSP, non-surveillance programme.
Surveillance vs non surveillance according to Child class

- Child-Pugh A
  \( P = 0.03 \)

- Child-Pugh B
  \( P = 0.001 \)

- Child-Pugh C
  \( P = 0.3 \)

Pascual S Liv Int 2006
Survival rate of HCC detected during follow-up and HCC detected in unscreened patients

Cumulative survival rates of hepatocellular carcinoma (HCC) detected during follow-up and HCC detected in unscreened patients. 1, HCC detected in surveilled patients (36 dead, 25 censored); 2, HCC detected in unsurveilled patients (95 dead, nine censored).
The role of α-fetoprotein in the surveillance of HCC

Chang T AJG 2015

<table>
<thead>
<tr>
<th>WHAT IS CURRENT KNOWLEDGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Surveillance of hepatocellular carcinoma (HCC) in high-risk patients can improve their outcomes and is recommended by all HCC guidelines.</td>
</tr>
<tr>
<td>✓ Ultrasound (US) has been the most widely accepted tool for HCC surveillance.</td>
</tr>
<tr>
<td>✓ The role of α-fetoprotein (AFP) in the surveillance of HCC remains controversial.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHAT IS NEW HERE</th>
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<tbody>
<tr>
<td>✓ Incorporating AFP into the HCC surveillance program for patients with cirrhosis improves the surveillance effectiveness.</td>
</tr>
</tbody>
</table>
Japanese experience: Fucosylated fraction of AFP (AFP-L3) fraction and prothrombin induced by vitamin K absence-II (PIVKA-II)

Receiver operating characteristic curves of α-fetoprotein-L3 and prothrombin induced by vitamin K absence-II for the diagnosis of hepatocellular carcinoma in patients with total α-fetoprotein < 20 ng/mL. The area under the curve values were 0.824 for α-fetoprotein (AFP)-L3, 0.774 for prothrombin induced by vitamin K absence (PIVKA)-II and 0.939 for the two combined markers.
Timing for surveillance
Every 6 or every 12 months?

*Observed survival of patients under semiannual or annual surveillance.*
The semiannual surveillance significantly increased the survival with respect to yearly program.
### Timing for surveillance

**Every 3 or every 6 months?**

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Population under surveillance</th>
<th>Test</th>
<th>Months</th>
</tr>
</thead>
</table>
| **EASL 2012** | Child-Pugh A or B cirrhotic  
Child-Pugh C cirrhotic awaiting liver transplantation  
Non-cirrhotic HBV carriers with active hepatitis or family history of HCC  
Non-cirrothc HCV chronic hepatitis with advanced liver fibrosis F3 | US | 6 |
| **JSH 2014** | **Super-high risk:**  
Hepatitis B-related liver cirrhosis  
Hepatitis C-related liver cirrhosis  
  
**High risk:**  
Non viral cirrhosis  
Non-cirrhotic HBV hepatitis  
Non-cirrhotic HCV hepatitis | US + AFP/PIVKA-II/AFP-L3 | 3  
US + AFP/PIVKA-II/AFP-L3 | 6 |
HCC surveillance in high risk and super high risk patients

• Evaluate the clinical impact of a 3-month enhanced surveillance compared to 6-month schedule in super high risk patients for HCC.

• Evaluate the role of different factors that may impact on survival.

• Estimate the economic impact of a 3-month surveillance in super high risk patients.

Courtesy of Peserico&Farinati on behalf of ITALICA 2017
Patients and methods

1,957 patients were selected from the multicenter ITA.LI.CA database from January 1986 to December 2014.

The inclusion criteria were:
- cirrhosis
- diagnosis under surveillance
- surveillance every 3 or 6 months

A subgroup of 1,576 patients who met Japanese guideline’s definition of “super-high risk” patients were extrapolated.
<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>Surveillance at 3 months</th>
<th>Surveillance at 6 months</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Super-high risk</td>
<td>194 (75%)</td>
<td>1382 (81%)</td>
<td>1576</td>
</tr>
<tr>
<td>High risk</td>
<td>66 (25%)</td>
<td>315 (19%)</td>
<td>381</td>
</tr>
</tbody>
</table>

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>260</td>
<td>1697</td>
<td>1957</td>
</tr>
</tbody>
</table>
## Super high risk patients

### Larger nodule size

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Surveillance at 3 months</th>
<th>Surveillance at 6 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 cm</td>
<td>67 (37.0%)</td>
<td>532 (42.3%)</td>
<td>ns</td>
</tr>
<tr>
<td>2 – 5 cm</td>
<td>101 (55.8%)</td>
<td>646 (51.4%)</td>
<td>ns</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>13 (7.2%)</td>
<td>79 (6.3%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

### Non-infiltrating monofocal nodules

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Surveillance at 3 months</th>
<th>Surveillance at 6 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 cm</td>
<td>46 (47.9%)</td>
<td>362 (46.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>2 – 5 cm</td>
<td>48 (50.0%)</td>
<td>383 (49.3%)</td>
<td>ns</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>2 (2.0%)</td>
<td>32 (4.1%)</td>
<td>ns</td>
</tr>
</tbody>
</table>
## Super high risk patients

### Multifocal nodules (2-3)

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Surveillance at 3 months</th>
<th>Surveillance at 6 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 cm</td>
<td>21 (25.9%)</td>
<td>163 (37.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>2 - 5 cm</td>
<td>51 (62.9%)</td>
<td>238 (55.1%)</td>
<td>ns</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>9 (11.1%)</td>
<td>31 (7.2%)</td>
<td>ns</td>
</tr>
</tbody>
</table>
## Super high risk patients

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Surveillance at 3 months</th>
<th>Surveillance at 6 months</th>
<th>p</th>
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<td>≤ 2 cm</td>
<td>21 (25.9%)</td>
<td>163 (37.7%)</td>
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<tr>
<td>2 - 5 cm</td>
<td>51 (62.9%)</td>
<td>238 (55.1%)</td>
<td>ns</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>9 (11.1%)</td>
<td>31 (7.2%)</td>
<td>ns</td>
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</tbody>
</table>

A 3-month surveillance did not improve the diagnosis of HCC in terms of tumor stage.
## Super high risk patients

### HCC Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Surveillance at 3 months</th>
<th>Surveillance at 6 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monofocal</td>
<td>98 (52.4%)</td>
<td>806 (61.4%)</td>
<td></td>
</tr>
<tr>
<td>Multifocal</td>
<td>83 (44.9%)</td>
<td>450 (34.3%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Infiltrating or massive</td>
<td>6 (3.2%)</td>
<td>56 (4.3%)</td>
<td></td>
</tr>
</tbody>
</table>

### Number of nodules

<table>
<thead>
<tr>
<th>Number of nodules</th>
<th>Surveillance at 3 months</th>
<th>Surveillance at 6 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99 (68.7%)</td>
<td>806 (76.9%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11 (7.6%)</td>
<td>119 (11.4%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11 (7.6%)</td>
<td>43 (4.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 4</td>
<td>23 (15.9%)</td>
<td>79 (7.5%)</td>
<td></td>
</tr>
</tbody>
</table>
### Milan Criteria in/out

<table>
<thead>
<tr>
<th></th>
<th>Surveillance at 3 months</th>
<th>Surveillance at 6 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>In</td>
<td>85 (64.4%)</td>
<td>755 (72.0%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Out</td>
<td>47 (35.6%)</td>
<td>293 (27.9%)</td>
<td></td>
</tr>
</tbody>
</table>

### HCC treatment

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Surveillance at 3 months</th>
<th>Surveillance at 6 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radical treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection/LT</td>
<td>103 (56.9%)</td>
<td>780 (60.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Ablation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Palliative treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE</td>
<td>68 (37.6%)</td>
<td>408 (31.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>3 (1.6%)</td>
<td>40 (3.1%)</td>
<td>ns</td>
</tr>
<tr>
<td>Palliative</td>
<td>7 (3.9%)</td>
<td>58 (4.5%)</td>
<td>ns</td>
</tr>
</tbody>
</table>
Survival in «super-high risk» patients according to 3- or 6-month surveillance

Cumulative survival

\[ p = 0.987 \]

Median survival

Surveillance at 3 months

35 months
(CI 95% 32 – 38)

Surveillance at 6 months

42 months
(CI 95% 37 – 43)
Microeconomic analysis

The average cost for the surveillance of a single «super-high risk» patient has been estimated considering the US cost of 80€ defined by the NHS. Data are expressed as expenses for a HCC diagnosed.

- Three-months surveillance: 3.327€
- Six-months surveillance: 1.880€

Difference: 1.447€
• Adherence was significantly higher:
  ➢ in cirrhotic patients compared to chronic hepatitis B.
  ➢ in EU compared to USA studies.
  ➢ in less than 12-month compared to yearly surveillance.

• Overall adherence rate to HCC surveillance was suboptimal at 52%.
Take home message

• Surveillance of HCC in patients with cirrhosis improve their outcome.
• Ultrasound is the most accepted tool but the incorporation of AFP improves the effectiveness.
• Biannual timing is recommended by European guidelines.
• Super-high risk patients should be managed as all other cirrhotic patients.
NASH Consensus Conference
Venice 15 February 2018

ILTS Annual Congress
Lisbon 23-26 May 2018

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