Hepatocellular Carcinoma Surveillance

Terry Wong
Consultant Hepatologist
Clinical Lead in Hepatology and Viral Hepatitis
Guys and St. Thomas’ Hospital
Hepatocellular Carcinoma Surveillance

• Why Survey?
• How to Survey?
• Who to Survey?
Incidence of Liver Cancer UK 1993-2016

Cancer Research UK 2019
European Incidence of Hepatocellular Carcinoma
Wilson-Jugner Criteria (WHO 1968)

- The condition being screened for should be an important health problem
- The natural history of the condition should be well understood
- There should be a detectable early stage
- Treatment at an early stage should be of more benefit than at a later stage
- A suitable test should be devised for the early stage
- The test should be acceptable
- Intervals for repeating the test should be determined
- Adequate health service provision should be made for the extra clinical workload resulting from screening
- The risks, both physical and psychological, should be less than the benefits
- The costs should be balanced against the benefits
Hepatocellular Carcinoma is Curable........

If treated early
“Milan” Criteria for Liver Transplantation

- 48 patients
- All had HCC
- All received OLT
- < 5cm single HCC
- ≤3 tumours <3cm
- 92% 4yr Disease Free survival

Survival After Resection for HCC

- Of 1265 HCC pts evaluated, only 35 were ideal candidates for resection.
Natural History of HCC

- Hepatocyte
- Biliocyte
- Stem cell (genomic alterations)

- Transformed cell

- HCC Ø 1-2 cm

- HCC Ø 4.5-8 cm

Serum Alpha-fetoprotein as surveillance
Accuracy of AFP

- Case-Control Study
- 170 HCC patients
- 170 Non HCC CLD patients
- Cut off of 20ng/ml
- 60.4% Sensitivity
- 99% Specificity


<table>
<thead>
<tr>
<th>AFP cut-off (ng/ml)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>62.4</td>
<td>89.4</td>
</tr>
<tr>
<td>20</td>
<td>60.0</td>
<td>90.6</td>
</tr>
<tr>
<td>100</td>
<td>31.2</td>
<td>98.8</td>
</tr>
<tr>
<td>200</td>
<td>22.4</td>
<td>99.4</td>
</tr>
<tr>
<td>400</td>
<td>17.1</td>
<td>99.4</td>
</tr>
</tbody>
</table>

\( ^{a} \) AFP, \( \alpha \)-fetoprotein; HCC, hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Patients ( (n) )</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg+ /anti-HCV-  (27)</td>
<td>59.3</td>
<td>85.2</td>
</tr>
<tr>
<td>HBsAg- /anti-HCV+ (103)</td>
<td>67.0*</td>
<td>89.3</td>
</tr>
<tr>
<td>HBsAg+ /anti-HCV+ (17)</td>
<td>58.8</td>
<td>94.1</td>
</tr>
<tr>
<td>HBsAg- /anti-HCV- (23)</td>
<td>30.4**</td>
<td>100.0</td>
</tr>
</tbody>
</table>

\( ^{a} \) AFP, \( \alpha \)-fetoprotein; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus. *\( P = 0.025 \) and **\( P = 0.011 \) vs. the overall sensitivity (hierarchical log-linear models).
AFP alone is insufficient as a screening test

- 5581 HBsAg positive males
- Randomised to 6 monthly AFP or observation
- No mortality difference between groups (when adjusted for lead time bias)

Liver Ultrasound as a Surveillance Tool
Accuracy of Ultrasound in the Detection of Hepatocellular Carcinoma at Any Stage

Sensitivity of U/S with and without AFP for Early Stage Hepatocellular Carcinoma
Frequency of Surveillance- Six monthly or twelve monthly?
Natural History of HCC

Molecular phase

Preclinical phase

Clinical (symptomatic) phase

Prediagnostic

Diagnostic

- Hepatocyte
- Biliocyte
- Stem cell (genomic alterations)

Transformed cell

HCC Ø 1-2 cm

HCC Ø 4.5-8 cm

### Tumour Doubling Time of Small (< 5cm ) HCC

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients</th>
<th>No HBsAg pos</th>
<th>Median doubling time (days)</th>
<th>Range (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheu 1985</td>
<td>28</td>
<td>23</td>
<td>117</td>
<td>29-398</td>
</tr>
<tr>
<td>Ebrara 1986</td>
<td>22</td>
<td>3</td>
<td>210</td>
<td>30-585</td>
</tr>
<tr>
<td>Okazaki 1989</td>
<td>15</td>
<td>2</td>
<td>102</td>
<td>41-305</td>
</tr>
<tr>
<td>Barbara 1992</td>
<td>39</td>
<td>11</td>
<td>171</td>
<td>27-605</td>
</tr>
<tr>
<td>Okada 1993</td>
<td>19</td>
<td></td>
<td>80</td>
<td>31-331</td>
</tr>
</tbody>
</table>
Six vs 12 monthly Surveillance

- 52823 HCC patients
- Divided into cohorts of HCC surveillance
- Increased mortality in the 12 monthly U/S vs 6 month cohorts (adjusted for lead time bias)
Six monthly vs 12 monthly Surveillance
Three monthly vs Six Monthly Surveillance

- 1278 cirrhotic patients
- 43 French sites
- Randomised to 3 monthly vs 6 monthly U/S
- End point HCC < 3cm
- No difference in incidence or prevalence of HCC < 3cm

Randomised Controlled Study of 6 monthly AFP+U/S

- 19200 patients
- HBsAg Positive
- Randomised to receive U/S+ AFP 6/12ly or observation
- 58% uptake
- HCC related mortality reduced in the screening arm (83.2 vs 131/100,000)


Fig. 4 Cumulative mortality from HCC in screening and control groups
UK Health Technology Assessment

- Cirrhotic patients
- HBV related cirrhosis most cost effective
- Most effective strategy 6/12ly U/S + AFP
How to Screen

• AASLD 2018
  • Six monthly U/S with or without AFP
  • Not possible to determine if U/S alone or U/S + AFP optimal
  • Optimal interval between 4 and 8 months
  • Not recommended to alter surveillance depending on aetiology or risk stratification

• EASL 2012
  • U/S Six monthly without AFP
  • Tumour biomarkers suboptimal (inc AFP)
  • Nodules< 1cm should have 4 monthly imaging for one year

• NICE 2016
  • Six monthly U/S with or without AFP
Cost Effectiveness

• Three month extension in life
• $50,000 per QALY
• In cirrhotic patients HCC incidence of 1.5%-6%= $26,000-$55,000 per QALY
• In Hepatitis B patients without cirrhosis 0.2% per annum

Who to Screen? AASLD 2018

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Threshold Incidence for Efficacy of Surveillance (≥0.25 LYG; % per year)</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian male hepatitis B carriers over age 40</td>
<td>0.2</td>
<td>0.4%-0.6% per year</td>
</tr>
<tr>
<td>Asian female hepatitis B carriers over age 50</td>
<td>0.2</td>
<td>0.3%-0.6% per year</td>
</tr>
<tr>
<td>Hepatitis B carrier with family history of HCC</td>
<td>0.2</td>
<td>Incidence higher than without family history</td>
</tr>
<tr>
<td>African and/or North American blacks with hepatitis B</td>
<td>0.2</td>
<td>HCC occurs at a younger age</td>
</tr>
<tr>
<td>Hepatitis B carriers with cirrhosis</td>
<td>0.2-1.5</td>
<td>3%-8% per year</td>
</tr>
<tr>
<td>Hepatitis C cirrhosis</td>
<td>1.5</td>
<td>3%-5% per year</td>
</tr>
<tr>
<td>Stage 4 PBC</td>
<td>1.5</td>
<td>3%-5% per year</td>
</tr>
<tr>
<td>Genetic hemochromatosis and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt;1.5% per year</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin deficiency and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt;1.5% per year</td>
</tr>
<tr>
<td>Other cirrhosis</td>
<td>1.5</td>
<td>Unknown</td>
</tr>
<tr>
<td>Surveillance benefit uncertain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B carriers younger than 40 (males) or 50 (females)</td>
<td>0.2</td>
<td>&lt;0.2% per year</td>
</tr>
<tr>
<td>Hepatitis C and stage 3 fibrosis</td>
<td>1.5</td>
<td>&lt;1.5% per year</td>
</tr>
<tr>
<td>NAFLD without cirrhosis</td>
<td>1.5</td>
<td>&lt;1.5% per year</td>
</tr>
</tbody>
</table>

Abbreviation: LYG, life-years gained.
### Table 3. Recommendations for HCC surveillance: categories of adult patients in whom surveillance is recommended.

1. Cirrhotic patients, Child-Pugh stage A and B*
2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation**
3. Non-cirrhotic HBV carriers with active hepatitis or family history of HCC***
4. Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3****

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*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.

• All cirrhotic patients

• Hepatitis B (NICE 2013)
  • If significant fibrosis - > F2 Metavir or F3 Ishak
  • If HBV VL > 20,000iu/ml and > 40yrs and FH of HCC
  • Do not survey if < F2/F3 and HBV DNA < 20,000iu/ml and < 40yrs
Hepatitis B and HCC Risk
High HBV viral load is associated with increased incidence of HCC

All participants (n=3,653)

Baseline HBV DNA Level (copies/mL)

≥10^6

10^5–<10^6

10^4–<10^5

300–<10^4

<300 (reference)

Cumulative incidence of HCC

Year of follow-up

0 1 2 3 4 5 6 7 8 9 10 11 12 13

p<0.001

p=0.06

Can we refine HCC surveillance in Hepatitis B?

- GAG-HCC
- CU-HCC
- REACH-B
- PAGE-B
- Majority developed in Asia
- Not validated in HBV-HIV-Co-infected

M.F. Yuen et al J Hepatol, 50 (2009), pp. 80-88
PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy

- 1815 patients receiving Entecavir/Tenfovir
- Derivation cohort of 1325 patient
- 5yr HCC risk
- PAGE-B≤9= 0% HCC

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Platelets (/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-29: 0</td>
<td>Female: 0</td>
<td>≥200,000: 0</td>
</tr>
<tr>
<td>30-39: 2</td>
<td>Male: 6</td>
<td>100,000-199,999: 6</td>
</tr>
<tr>
<td>40-49: 4</td>
<td></td>
<td>&lt;100,000: 9</td>
</tr>
<tr>
<td>50-59: 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69: 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70: 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Papatheodoridis G et al J Hepatol. 2016 Apr;64(4):800-6
Hepatitis C and HCC Risk
HCC Risk With IFN or DAAs

- Clearly a benefit in those who achieve SVR
- Curves look fairly similar

HCC Risk in Hepatitis C According to Transient Elastography

- 866 patients
- 3yr follow up

Fig. 1. Cumulative incidence of HCC development stratified based on LSM (N = 866). LSM, liver stiffness measurement.
### What About HCC Surveillance?

<table>
<thead>
<tr>
<th>Guideline/Guidance</th>
<th>F0-F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD/IDSA (HCV)</td>
<td>Same as for those never infected with HCV</td>
<td>Ultrasound every 6 mos</td>
<td></td>
</tr>
<tr>
<td>EASL</td>
<td>None</td>
<td>Ultrasound every 6 mos</td>
<td></td>
</tr>
<tr>
<td>AASLD/IDSA (HCC)</td>
<td>None</td>
<td>None (incidence &lt; 1.5%/yr)</td>
<td>Ultrasound every 6 mos (incidence 3% to 5%/yr)</td>
</tr>
</tbody>
</table>

How Accurate Is Transient Elastography to Monitor for Regression of Cirrhosis After SVR?


33 pts with HCV and biopsy-proven cirrhosis who achieved SVR after IFN based therapy

<table>
<thead>
<tr>
<th>FibroScan and biopsy ~ 60 mos post SVR</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 pts regressed (≤ F3)</td>
<td></td>
</tr>
<tr>
<td>13 pts had persistent cirrhosis (F4)</td>
<td></td>
</tr>
</tbody>
</table>

- Diagnostic accuracy of TE for diagnosing post-SVR cirrhosis: 61% sensitivity, 95% specificity
- Regression of Fibroscan scores to “sub-cirrhotic” levels does not ensure true cirrhosis regression

HCC Risk Remains After Fibrosis Regression in HCV

- 29033 patients who received DAAs
- 19102 patients who received IFN
- Followed up for average 5 yrs
- 1509 HCCs detected

Ioannou G et al Gastroenterology 2019 (in press)
AASLD/IDSA Recommendations on Monitoring Fibrosis Regression in Pts Achieving SVR

- Risk of HCC in pts with advanced pretreatment fibrosis who demonstrate regression to minimal fibrosis post treatment is not known
- Such pts should continue to be monitored for HCC regularly
- No recommendations for routine assessment for regression in liver fibrosis after achieving SVR
What is the Influence of HIV on HCC?
Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies

- 3625 patients
- Overall HCC incidence 0.59% in cirrhotic and 0.12% in non-cirrhotics
- Below screening threshold in non-cirrhotics who started TDF < 46yrs
- Two patients with a PAGE-B <10 developed HCC

Influence of HIV Infection on the Natural History of Hepatocellular Carcinoma: Results From a Global Multicohort Study

BHIVA Guidance

- We recommend HCC screening with 6-monthly ultrasound (1A) and suggest 6-monthly serum alphafetoprotein (AFP) (2C) should be offered to all cirrhotic patients with HBV/HIV and HCV/HIV infection.

- We suggest all non-cirrhotic patients with HBV/HIV infection should be screened for HCC six monthly.
Summary

- Screen all cirrhotics for hepatocellular carcinoma
- Hepatitis B - Screen all cirrhotics, and some non-cirrhotics
- Hepatitis C - screen all patients who are cirrhotic prior to therapy, even if cirrhosis regresses
- Non-cirrhotic HBV-HIV-? Screen all patients
- Screen with six monthly alphafetoprotein and ultrasound