HCC in HIV
who and how to screen

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Guidelines for the management of Hepatocellular Carcinoma

There are no specific recommendations for HIV patients.
HCC in HIV: who and how to screen

Outline

- Hepatocellular carcinoma epidemiology
- Screening and surveillance
- Diagnosis of HCC
- Staging of HCC
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In 2015, 559,000 men and 233,000 women were estimated to have a HCC accounting for the second leading cause of cancer death in men and the fifth in women, worldwide.
Among 615,150 individuals with AIDS, HCC risk was elevated almost 4 times compared with the risk in the general population.
Incidence of Hepatocellular Carcinoma in HIV-Infected Patients With Cirrhosis: A Prospective Study

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<table>
<thead>
<tr>
<th>Study Group</th>
<th>No. HCC/No. Patients at Risk</th>
<th>Cumulative Incidence % (95% CI)</th>
<th>Incidence Rate No. HCC Per 1000 Person-Years (95% CI)</th>
<th>Rate Ratio Incidence Rate Exposed/Incidence Rate Nonexposed (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Decompensation of cirrhosis at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Decompensated</td>
<td>5/276</td>
<td>1.8 (0.6–4.2)</td>
<td>4.0 (0.5–7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensated</td>
<td>595</td>
<td>5.26 (1.7–11.9)</td>
<td>20.0 (2.5–37.5)</td>
<td>5.0 (1.1–21.5)</td>
<td>0.032</td>
</tr>
<tr>
<td>HCV coinfection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic HCV</td>
<td>9/354</td>
<td>2.5 (1.2–4.8)</td>
<td>6.3 (2.2–10.4)</td>
<td>0.3 (0.04–2.6)</td>
<td>0.610</td>
</tr>
<tr>
<td>Absent or cured</td>
<td>1/16</td>
<td>6.3 (0.2–30.2)</td>
<td>18.7 (−18.0–55.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic HBV</td>
<td>1/29</td>
<td>3.5 (0.1–17.8)</td>
<td>10.1 (−9.7–29.8)</td>
<td></td>
<td>1.000</td>
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<tr>
<td>HBV coinfection</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Absent, postvaccination, cured, or core</td>
<td>8/305</td>
<td>2.6 (1.1–5.1)</td>
<td>6.6 (2.0–11.1)</td>
<td>1.5 (0.04–11.5)</td>
<td></td>
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</tbody>
</table>
Risk factors for HCC in HIV patients

HCC is more common in HIV+ than in general population because of higher prevalence of risk factors:\n\[1\]:
- Viruses (HBV, HCV, HDV)
- Alcohol abuse \[2\]
- Insulin resistance/NASH,NAFLD
- HIV-1 Tat gene
- High rate of cirrhosis

Patients with HCC have High Mortality Compared With Other Common Cancers

- 5-yr survival from diagnosis of liver cancer overall is 15%
- The only common cancer with worse overall prognosis is pancreatic cancer (6%)

Unlike HCV-infected patients with cirrhosis, patients with cirrhosis coinfected with HIV and HCV frequently present at radiologic diagnosis with infiltrative-type HCC and portal-obstructing tumors, which results in dramatically shorter survival.
Survival of HCC is strongly related to stage at diagnosis.

Earlier detection of HCC could improve outcome.
Screening for Hepatocellular Carcinoma (HCC) in HIV/HCV-Coinfected Patients: Impact on Survival

At Risk

<table>
<thead>
<tr>
<th></th>
<th>HCC Screen</th>
<th>No HCC Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>12 months</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>24 months</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>36 months</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>48 months</td>
<td>1</td>
<td>0</td>
</tr>
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</table>

**Actuarial median survival:**

- **HCC screen**: 12.8 months
- **No HCC screen**: 3.7 months

Brau N et al. CROI 2010
Why Is HCC So Lethal?

- Cirrhosis is often not diagnosed
- Evolves silently, often in multiple foci
- Progresses to invade vessels
- Spreads via both blood and lymph
- *Rarely produces symptoms until advanced stage*
- Most are diagnosed late
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Screening is the application of a test to detect a disease in a population which has no signs or symptoms of that disease, while surveillance is the periodic repetition of the screening test in the same population.

Positive findings of screening or surveillance tests must entrain a pre-defined recall policy aimed at identifying true positive cases with additional diagnostic procedures.
WHO SHOULD BE SURVEILLED?

- In the Western world, surveillance is recommended for subjects at high risk of developing HCC such as patients with cirrhosis and certain categories of patients with chronic hepatitis.

- Japanese guidelines extend this recommendation to all patients with chronic hepatitis.

- An essential pre-requisite to perform surveillance is the absence of contraindications to treatment either curative or palliative.
High-risk groups for hepatocellular carcinoma (HCC) in whom surveillance might be indicated

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>HCC risk per year</th>
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<tbody>
<tr>
<td>Hepatitis C</td>
<td>2–7%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3–5%</td>
</tr>
<tr>
<td>Genetic hemochromatosis</td>
<td>NA</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>2–3%</td>
</tr>
<tr>
<td>Non alcoholic steatohepatitis</td>
<td>NA</td>
</tr>
<tr>
<td>Alpha 1 antitrypsin deficiency, autoimmune hepatitis</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatitis B carriers without cirrhosis (HBV surface Ag+)</th>
<th>HCC risk per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian males &gt;40 years of age</td>
<td>0.4–0.6</td>
</tr>
<tr>
<td>Asian females &gt;50 years of age</td>
<td>0.3–0.6</td>
</tr>
<tr>
<td>Africans &gt;20 years of age</td>
<td>NA</td>
</tr>
<tr>
<td>Family history of HCC</td>
<td>NA</td>
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</tbody>
</table>
Surveillance Imaging for HCC

- Ultrasound is the usual modality for HCC surveillance and detection
- Advantages: cheap, safe, supported by data
- Drawbacks: operator dependent, limited sensitivity, difficult in obese patients

Sonogram shows a small hypoechoic mass

Surveillance Interval

- The HCC surveillance interval is based on the expected tumor growth rate in cirrhosis.

- The median doubling time of an HCC lesion is reported to be 117 days (range, 29-398 days).

- The available evidence suggests that 6 months is the optimal HCC surveillance interval.

Surveillance EASL guidelines

- Implementation of surveillance programs to identify at-risk candidate populations and identification of biomarkers for early HCC detection are a major public health goal to decrease HCC-related deaths (evidence 1D; recommendation 1B) Government health policy and research agencies should address these needs

- Patients at high risk for developing HCC should be entered into surveillance programs. Groups at high risk are depicted in Table 3 (evidence 1B/3A; recommendation 1A/B)

- Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 months (evidence 2D; recommendation 1B)

  Exceptions: A shorter follow-up interval (every 3-4 months) is recommended in the following cases:
  1. Where a nodule of less than 1 cm has been detected (see recall policy), 2. In the follow-up strategy after resection or loco-regional therapies (evidence 3D; recommendation 2B)

- Accurate tumor biomarkers for early detection need to be developed. Data available with tested biomarkers (i.e. AFP, AFP-L3 and DCP) show that these tests are suboptimal for routine clinical practice (evidence 2D; recommendation 2B)

- Patients on the waiting list for liver transplantation should be screened for HCC in order to detect and manage tumor progression and to help define priority policies for transplantation (evidence 3D; recommendation 1B)
Recall policy EASL guidelines

- In cirrhotic patients, nodules less than 1 cm in diameter detected by ultrasound should be followed every 4 months the first year and with regular checking every 6 months thereafter (evidence 3D; recommendation 2B)

- In cirrhotic patients, diagnosis of HCC for nodules of 1-2 cm in diameter should be based on non-invasive criteria or biopsy-proven pathological confirmation. In the latter case, it is recommended that biopsies are assessed by an expert hepatopathologist. A second biopsy is recommended in case of inconclusive findings, or growth or change in enhancement pattern identified during follow-up (evidence 2D; recommendation 1B)

- In cirrhotic patients, nodules more than 2 cm in diameter can be diagnosed for HCC based on typical features on one imaging technique. In case of uncertainty or atypical radiological findings, diagnosis should be confirmed by biopsy (evidence 2D; recommendation 1A)
The role of a-fetoprotein levels

- The latest Western guidelines for the clinical management of HCC dropped AFP from the screening and surveillance armamentarium, because it was proven to be both not sensitive enough to identify early stage HCC and not specific enough to avoid unnecessary recall procedures.

- Nevertheless, despite this compelling evidence, the use of serum AFP in the surveillance of HCC is a “hard-to-die”
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HCC Diagnosis: Dynamic Imaging

- HCCs are hypervascular
- Tumor blood supply:
  - 100% hepatic artery
- Liver parenchymal blood supply:
  - 30% hepatic artery
  - 70% portal vein

- Diagnosis of HCC is based on non-invasive criteria or pathology (evidence 2D; recommendation 1A)
- Pathological diagnosis of HCC is based on the recommendations of the International Consensus Panel. Immunostaining for GPC3, HSP70, and glutamine synthetase and/or gene expression profiles (GPC3, LYVE1 and survivin) are recommended to differentiate high grade dysplastic nodules from early HCC (evidence 2D; recommendation 2B).
  Additional staining can be considered to detect progenitor cell features (K19 and EpCAM) or assess neovascularisation (CD34).
- Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1 cm in diameter (evidence 2D; recommendation 2B), a more conservative approach with 2 techniques is recommended in suboptimal settings. The role of contrast-enhanced ultrasound (CEUS) and angiography is controversial. PET-scan is not accurate for early diagnosis.
CEUS IN HCC GUIDELINES AROUND THE WORLD

CEUS ACCEPTED FOR DIAGNOSIS OF HCC?

- **AASLD** (published 2005, updated 2011)
  USA
  NO

- **EASL** (2012)
  EASL. J Hepatol 2012;56:908-943
  Europe
  NO
  The role of CEUS is controversial

- **APASL** (2010)
  Asia/Pacific
  YES

- **JSH** (2011)
  Kokudo N, Hepatology Research, 2015;45:123-127
  Japan
  YES

- **WFUMB-EFSUMB** (ultrasound societies) (2013)
  Claudon M, Dietrich CF. Ultraschall Med 2013;34:11-29
  World/Eu
  YES

- **AISF** (2013)
  AISF expert panel. Dig Liver Dis 2013;45:712-723
  Italy
  YES
EASL - HCC guidelines: The biopsy role

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Staging of HCC: The ABCs

- Prognosis of HCC and treatment options are determined by
  - Anatomical extent of tumor (stage)
  - Biological aggressiveness (grade)
  - Cirrhosis severity and functional status

- BCLC staging system combines anatomic extent of disease with severity of liver failure (CTP class) and functional status
BCLC staging system and treatment strategy - EASL guidelines

- **Pts at Risk, n**
  - Stage A: 64, 51, 25, 8
  - Stage B: 60, 22, 11, 4
  - Stage C: 76, 10, 3, 1
  - Stage D: 39, 7, 1, 0

- **Survival Probability**

- **BCLC stage D** has poorest survival and few treatment options

- PST: performance status
Conclusions

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

- Ultrasound is the usual modality for HCC surveillance and detection

- The available evidence suggests that 6 months is the optimal HCC surveillance interval

- All guidelines accept a non invasive diagnosis of HCC by CT or MRI when showing wash-in and wash-out

- The correct diagnosis is crucial for the allocation of the patients to the best therapy

- Considering the prognosis of HIV - HCC patients, effective screening techniques, programs, and specific management is mandatory.