Screening for Hepatoma and an Introduction to LIRADS

Helena Gabriel, MD
Associate Professor of Radiology
Director, School of Ultrasound
Northwestern University
Feinberg School of Medicine
Chicago, IL

Overview

• HCC: the problem
• Principles of screening: is screening efficacious?
• Evidence for screening
• Findings of HCC on US, CT/ MR, US contrast based on molecular and vascular tumor features
• LIRADS: explanation and image examples
• How US fits into LIRADS and screening

Hepatocellular Carcinoma, A World-Wide Problem

• Incidence varies strikingly by geography
• Global variations in incidence reflect variation in risk factors for HCC, namely HBV and HCV

GLOBOCAN, World Health Organization
Global Hepatoma Incidence Map 2012

GLOBOCAN, WHO. Global Hepatoma Incidence Map: Hepatitis B Prevalence Overlay

GLOBOCAN, WHO. Global Hepatoma Incidence Map: Hepatitis C Prevalence Overlay
Age-standardized incidence and mortality rates of liver cancer (per 100,000 persons) in different world regions

- China: 350
- South: 200
- East Asia: 100
- European Union: 50
- Africa: 25
- US: 15
- World: 10

Liver cancer incidence (Per 100,000)

- South: 67
- East Asia: 62
- European Union: 47
- Africa: 46
- US: 44
- World: 42

Hepatoma incidence and mortality

- Fifth most common cancer in men, seventh in women.
- Mortality: Second highest in males, sixth highest in females, overall third most common cause of death worldwide.
- Incidence/mortality ratio of 1.07 suggests it is a lethal disease, most people die of disease if no intervention.

HCC mortality: Barcelona clinic liver cancer (BCLC) staging vs. survival

- BCLC is most commonly used staging system for HCC.
- BCLC takes into account tumor stage, liver function, physical status and symptoms and links the stages with treatment algorithm.
- Natural history of disease/prognosis is dismal if there is no intervention/treatment.

Survival, according to tumor stage, in untreated HCC

- Intermediate stage
- Advanced stage

Hepatoma

- There is a world-wide “epidemic” which has geographical variation based on risk factors.
- Incidence continues to increase.
- Mortality if untreated is dismal.
- Hepatoma is a major world-wide health concern.

Age-adjusted incidence rates of liver cancer (per 100,000) in the United States

- All races: 10
- Whites: 8
- Blacks: 6
- Asians: 4
- Hispanics: 2

Survival probability (Percent)

- Survival, according to tumor stage, in untreated HCC

- Survival, according to tumor stage, in untreated HCC

- Survival, according to tumor stage, in untreated HCC
Should there be world-wide screening, surveillance for hepatoma?

- AASLD (American Association for Study of Liver Disease)
- EASLD (European Association for Study of Liver Disease)
- AASLD guideline provides an excellent data, evidence-based approach to diagnosis, staging and treatment of patient with HCC. Provides data-supported recommendations
- AASLD, EASLD very similar except for a few small points

Principles of effective population screening, World Health Organization

- The disease should be common with significant mortality and morbidity
- The disease should have a latent or early symptomatic stage
- There should be a target population for screening
- The test should have high sensitivity and specificity and be acceptable to patient
- There should be standardized recall procedures
- There should be facilities available for recall procedures and tx
- The disease must have effective therapy that can decrease mortality if the disease is detected early enough
- The test should decrease disease-specific mortality
- Cost of screening should be economically balanced

Screening for Hepatoma—Identifying an at risk population

- At risk population is dependent on incidence
- From prior graphs, distribution of HCC worldwide mirrors Hepatitis B, C infection
- Prospective trials have shown that if the incidence of HCC is 1.5%/year or greater, surveillance helpful, Sarasin et al. and Lin et al.

Screening for Hepatoma: Identification of an at-risk patient population

- Risk factors for hepatoma: 75% due to hepatitis B, C infection:
  - Risk with Hepatitis B
    - Most common cause of HCC in low resource countries
    - Annual incidence of HCC in patients with hepatitis B: 0.5-1.0%/year in Asia
    - Relative risk of HCC in patients with hepatitis B 100 x
    - Range in US varies
    - Risk increases with onset of cirrhosis
  - Risk with Hepatitis C
    - Most common cause of HCC in Western countries
    - Relative risk 20 x
    - Highest risk with cirrhosis-inc of HCC 2-8%/year

Screening for Hepatoma—Decreased Mortality?

- Disease that is potentially treatable/curable
- Screening has shown decrease in mortality
- SEER data has shown other endpoints such as downgrading in stage or 5 year mortality rates not valid endpoints due to lead and length time bias
- One RCT (randomized controlled trial) in Shanghai, Zhang et al, evaluated the use of screening/surveillance US and AFP.
  - 18,816 patients who underwent 6 mo AFP and US surveillance.
  - 37% reduction in HCC related mortality even with poor compliance (60% adherence to screening protocol)
study profile

- Randomization: 19200 subjects aged 25-59 years with HBV-M (+) or chronic hepatitis

- Screening group: 9757

- Control group: 9443

- Not told, no screening

- December 1997: 67 patients with HCC

- December 31, 1997: 54 died from HCC

- December 1997: 69 patients with HCC

- December 31, 1997: 32 died from HCC

- First round screening: 17 patients with HCC

- Agree to participate: 9373

- Refuse to participate: 384

Cumulative mortality from HCC in screening and control groups

Screening for HCC: decrease in mortality

- Second China study did not show a decrease in mortality but smaller and not as well regarded

- Other prospective trials needed but will likely not be performed since most feel surveillance is helpful and not ethical to not provide surveillance

Screening in HCC: decrease in mortality

- Other cohort studies show improved survival with HCC screening.

  - McMahon B. Hepatology. 2000

- Surrogate endpoint: detection of HCC at an earlier stage when curative treatment possible.


How Well does the Screening Modality Perform? Adequate Sensitivity, Specificity, Accuracy

- Does the test have adequate sensitivity, specificity, accuracy (positive and negative predictive values) and performance characteristics (ROC curves)

  Serological
  - AFP
  - DCP
  - Lectin-bound AFP
  - TIE2

  Radiological screening
  - US
  - CT
  - MR
  - US contrast

Surveillance Tests-AFP

- AFP is a glycoprotein secreted by fetal hepatocytes and HCC (poorly differentiated)

- Pitfalls of AFP: AFP can be high in chronic liver disease and not all HCCs secrete AFP

- ROC analysis of AFP suggest 20 ng/mL is the best cut off

- At this level, sensitivity of AFP for HCC 60%

- HALT-C study: studied efficacy of interferon and looked at AFP levels, AFP levels inadequate for surveillance detection of HCC

- AFP inadequate screening test for HCC

- Better as a diagnostic rather than screening test?

- Other serologic tests-DCP and others- ineffective
Very few studies evaluating in the context of screening

Higher sensitivity for absolute lesion detection than US

New updated AASLD guideline, “AFP determination lacks adequate sensitivity and specificity for effective surveillance (and for diagnosis). Thus, surveillance has to be based on ultrasound examination.”

Sensitivity for HCC ranges from 30-100%, Specificity 73-100%

Singal et al. Aliment Pharmacol Ther 2009

- Meta-analysis of surveillance US for HCC in patients with cirrhosis
- 94% any stage
- 63% early stage
- Addition of AFP not helpful in HCC detection, 63%–69%, not statistically significant
- Screening at 6 month rather than 1 year intervals improved sensitivity (50.1% v 70.1%)
- Screening interval should be based on tumor growth rate and doubling times; median HCC doubling time is 170 days.
- AASLD recommends a screening interval of 6 months

Screening with CT/MR

- Original AASLD guidelines suggested US with AFP as per the China study
- Sensitivity for HCC ranges from 30-100%, Specificity 73-100%
- Singal et al. Aliment Pharmacol Ther 2009
  - Meta-analysis of surveillance US for HCC in patients with cirrhosis
  - 94% any stage
  - 63% early stage
  - Addition of AFP not helpful in HCC detection, 63%–69%, not statistically significant
  - Screening at 6 month rather than 1 year intervals improved sensitivity (50.1% v 70.1%)
  - Screening interval should be based on tumor growth rate and doubling times; median HCC doubling time is 170 days.
  - AASLD recommends a screening interval of 6 months

Is screening modality cost effective?

- Level considered cost effective is interventions achieved at a cost of $50,000/year of life gained
- Cost effectiveness dependent on incidence
- Screening for HCC is cost effective if risk of HCC is 1.5%/year or greater, AASLD.
- Lin et al found US screening for HCC cost effective despite incidence
Is there effective treatment for HCC?

BCLC (Barcelona Clinic Liver Cancer): Staging & treatment allocation algorithm

- Very early stage (0) Single < 2 cm, carcinoma in situ
- Early stage (A) Single or 3 nodules ≤ 3 cm, PS 0
- Intermediate stage (B) Multinodular, PS 0
- Advanced stage (C) Portal invasion, N1, M1, PS 1 - 2
- Terminal stage (D) TACE

AASLD guidelines

- Patients at high risk for developing HCC should be entered into surveillance programs
- Surveillance for HCC should be performed with ultrasonography
- AFP is an inadequate screening test for HCC and is not recommended
- Patients should be screened at 6 month intervals
- Surveillance interval does not need to be shortened for patients at higher risk of HCC

Screening for Hepatoma Conclusions:

- Can be performed in at risk patients with cirrhosis
- Has been shown to decrease mortality
- US has been shown to be effective, CT/MR not validated in RCTs
- Can be cost-effective with US
- Natural course of disease can be altered by effective tx
- Recommended by the AASLD, EASLD and Barcelona guidelines

AASLD guidelines

- Patients at high risk for developing HCC should be entered into surveillance programs
- Surveillance for HCC should be performed with ultrasonography
- AFP is an inadequate screening test for HCC and is not recommended
- Patients should be screened at 6 month intervals
- Surveillance interval does not need to be shortened for patients at higher risk of HCC

Imaging Findings of Hepatoma: Ultrasound

- Single vs multiple vs infiltrating
- Echogenicity varies, Ignee, et al. Z Gastroenterol, 2005, 100 histo-proven cases:
  - Hypoechoic (48%), isoechoic (9%), hyperechoic (19%), mixture (25%)
  - Well-defined or poorly defined
- Hypoechoic halo may represent a fibrous capsule
- Additional finding: PV invasion, stellate scar, calcification
- Vascularity: Hypervascular with penetrating branching appearance. Contrast increases vascularity
- Limitations in cirrhotic liver

Imaging Findings of HCC:

- Findings seen with contrast-enhanced imaging reflect some of the changes seen with hepatocarcinogenesis of hepatic nodules.
- Hepatocarcinogenesis is the transformation of normal hepatocytes to malignant nodules, HCC that involves many factors:
  - Molecular level-genetic alterations
  - Structural level-genetic mutations, transpositions, deletions
  - Pathologically, desdifferentiation of hepatocytes to abnormal nodules
  - Angiogenesis - unpaired arteries and sinusoidal capillarization, decrease in portal tracts
  - Vascular drainage changes from HVs to PVs and sinusoids
  - Tumor capsule and fibrous septa
  - Fat deposition
  - Increase in OATP expression
  - Iron resistance

Findings of Hepatoma on CT, MR, contrast US

- Findings seen with contrast-enhanced imaging reflect some of the changes seen with hepatocarcinogenesis of hepatic nodules.
Hemodynamic and OATP expression changes during multistep hepatocarcinogenesis

- Cirrhotic Islets
- Low-grade dysplastic Islets
- High-grade dysplastic Islets
- Early HCC
- Progressed HCC

OATP expression

Adapted from Choi et al., CT and MR Imaging: Diagnosis and Staging of Hepatocellular Carcinoma: Part I Radiology 2014

Imaging correlates to hepatocarcinogenesis: cirrhotic nodule

- Most cirrhotic nodules are imperceptible and blend with parenchymal background
- T1W isointense, rarely hyperintense (mechanism unknown)
- T2W iso to hypointense
- Postcontrast is to hypointense (relative to adjacent delayed enhancing fibrosis). Normal portal triads and OATP expression is preserved-similar signal intensity to liver in hepatobiliary phase.
- Slightly atypical features: T1 hyperintensity, delayed relative hypoenhancement, hepatobiliary phase hypointensity

Imaging correlates to hepatocarcinogenesis: Dysplastic nodule

- Hyperintense on T1W- Iron or Copper
- Hypo or Iso on T2W (never hyperintense)-may contain iron
- Post contrast-is (most have portal triads), some have neovascularity and are hyperintense on contrast.
- No washout, no capsular appearance-drainage patterns have not changed.

Imaging correlates to hepatocarcinogenesis: HCC

- Early HCC
  - Fat deposition-fewer arteries and veins may cause ischemia in the nodule and fatty reactive change
  - Non-iron containing
  - May have arterial hypervascularity, may have washout

- Progressed HCC
  - Arterial hypervascularity- unpaired arteries and sinusoidal capillarization
  - Portal venous and delayed phase washout-drainage patterns changed to portal veins and sinusoids
  - T2W hyperintensity, may be iso or hypo as well
  - Tumor capsule and fibrous septae
  - Corona radiata

AASLD: Diagnostic algorithm for suspected HCC

- Nodules of concern should be followed with abdominal MR or CT with contrast where possible for 2 years, unless the lesion worsens sooner.
- Nodules <1 cm should be followed with ultrasound every 3-6 months. If no growth for 2 years, revert to routine surveillance.
- For nodules >1 cm, typical imaging appearance is diagnostic. Otherwise, a second study with the other imaging modality should be performed, or the lesion biopsied.
### Hepatoma distant metastases
- Lung, intra-abdominal lymph nodes, bone, adrenal glands
- Porta hepatis nodes often seen and benign
- Pelvic bones often the site of bone metastases

### LI-RADS (v. 2013)

<table>
<thead>
<tr>
<th>Observation</th>
<th>Benign entity</th>
<th>Definite</th>
<th>Probable</th>
<th>Neither definite nor probable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LR1</td>
<td>LR2</td>
<td>LR3</td>
</tr>
</tbody>
</table>

### LI-RADS (v. 2014)

<table>
<thead>
<tr>
<th>Observation in high risk patient</th>
<th>LR5V</th>
<th>LR-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite with high likelihood of malignancy</td>
<td>LR-1</td>
<td>LR-1</td>
</tr>
<tr>
<td>Non-HCC malignancy</td>
<td>LR-2</td>
<td>LR-2</td>
</tr>
<tr>
<td>Tumor in vein?</td>
<td>LR-3</td>
<td>LR-3</td>
</tr>
</tbody>
</table>

### Conclusions
- Hepatoma is an epidemic with geographic variations that reflect variations in risk factors, namely Hepatitis B, C
- Screening for hepatoma decreases mortality and should be performed according to the tenets of screening
- Ultrasound is the only screening/surveillance modality which has been proven to decrease mortality in a large RCT.