AASLD Guidelines and HCC: a US based commentary

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Senior Medical Director
Professor of Clinical Medicine University of Nevada
Lung Mortality from Common Malignancies in US

## Estimated Deaths from Cancer Worldwide by Rank

<table>
<thead>
<tr>
<th>Cancer ranking</th>
<th>Men</th>
<th>No.</th>
<th>Cancer ranking</th>
<th>Women</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Lung and bronchus</td>
<td>951,000</td>
<td>1.</td>
<td>Breast</td>
<td>458,400</td>
</tr>
<tr>
<td>2.</td>
<td>Liver</td>
<td>478,300</td>
<td>2.</td>
<td>Colon and rectum</td>
<td>288,100</td>
</tr>
<tr>
<td>3.</td>
<td>Stomach</td>
<td>464,400</td>
<td>3.</td>
<td>Cervix uteri</td>
<td>275,100</td>
</tr>
<tr>
<td>4.</td>
<td>Colon and rectum</td>
<td>320,600</td>
<td>4.</td>
<td>Lung and bronchus</td>
<td>427,400</td>
</tr>
<tr>
<td>5.</td>
<td>Esophagus</td>
<td>276,100</td>
<td>5.</td>
<td>Stomach</td>
<td>273,600</td>
</tr>
<tr>
<td>6.</td>
<td>Prostate</td>
<td>258,400</td>
<td>7.</td>
<td>Liver</td>
<td>217,600</td>
</tr>
<tr>
<td>7.</td>
<td>Leukemia</td>
<td>143,700</td>
<td>8.</td>
<td>Ovary</td>
<td>140,200</td>
</tr>
<tr>
<td>9.</td>
<td>Bladder</td>
<td>112,300</td>
<td>10.</td>
<td>Leukemia</td>
<td>113,800</td>
</tr>
<tr>
<td>10.</td>
<td>Non-Hodgkin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**695,900 liver cancer deaths**

All sites but skin: 3,345,800

GLOBCAN 2008
New AASLD HCC Guidelines are in process of being written:

- Proposal

- We are the world

- Need to look at HCC as a global disease and recognized the diversity of disease and resources throughout the world
Table 2. Definitions

- Screening—application of diagnostic tests in patients at risk for HCC, but in whom there is no a priori reason to suspect that HCC is present.
- Surveillance—the repeated application of screening tests.
- Enhanced follow-up—the series of investigations required to confirm or refute a diagnosis of HCC in patients in whom a surveillance test result is abnormal. In addition to the use of additional diagnostic tests the interval between assessments is shorter than for surveillance since there is a concern that a cancer already exists.
- Lead-time bias—This is the apparent improved survival that comes from the diagnosis being made earlier in the course of a disease than when the disease is diagnosed because of the development of symptoms. Unless properly controlled, studies of surveillance will show enhanced survival simply because the cancer is diagnosed at an earlier stage.
- Length bias—This is the apparent improvement in survival that occurs because surveillance preferentially detects slow growing cancers. More rapidly growing cancers may grow too large to be treated between screening visits.
## AASLD Recommendations for HCC Surveillance

<table>
<thead>
<tr>
<th>HBV carriers</th>
<th>Non HBV-cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cost effective if risk &gt;0.2%/y)</td>
<td>(Cost effective if risk &gt;1.5%/y)</td>
</tr>
<tr>
<td>➤ Asian M≥40y, F≥50y</td>
<td>➤ HCV</td>
</tr>
<tr>
<td>➤ Africans/Af Am &gt;20yo</td>
<td>➤ Alcoholic cirrhosis</td>
</tr>
<tr>
<td>➤ Family history of HCC</td>
<td>➤ Genetic hemochromatosis</td>
</tr>
<tr>
<td>➤ Cirrhosis</td>
<td>➤ Primary biliary cirrhosis</td>
</tr>
</tbody>
</table>

**Increased risk but insufficient data to recommend surveillance**

- Alpha1-antitrypsin
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis

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The USPSTF recommends screening for HCV infection in persons at high risk for infection. The USPSTF also recommends offering 1-time screening for HCV infection to adults born between 1945 and 1965.

Benefits of Birth Cohort Screening

- Projected reduction in Incidence among Americans born 1946-1970

Reduction of HCC with IFN for HCV

Meta-analysis in cirrhotics

Hepatitis C patients achieving SVR was 3.7* times less likely to develop HCC than non-SVR patients.

*95% confidence interval 1.7-7.8

**Sofosbuvir + RBV**

**VALENCE: Genotype 2,3 IFN naïve, ineligible or treatment failures**

- **G2**
  - SOF+RBV (n=73)
  - SVR12 = 93%
- **G3**
  - SOF+RBV (n=250)

**Genotype 3**

- **Wk 0**
  - 93/92
  - 92/13
  - 85/100
  - 27/45

- **Wk 24**
  - FDA Advisory Committee Meeting, Oct 25, 2013; Zeuzem S et al, AASLD 2013, #1085
Need to update who needs surveillance and when

- NASH is the next HCV/HBV
Estimating Risk of HCC

- UNOS data (2002-2011):
- Incidence of de novo HCC on waitlist

Prevalence of NAFLD

Liver histology in autopsies of descendants from non-natural causes (n=465, 1981-2010)

<table>
<thead>
<tr>
<th></th>
<th>81-90</th>
<th>91-00</th>
<th>01-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BMI</td>
<td>23.9</td>
<td>26.5</td>
<td>27.8</td>
</tr>
<tr>
<td>Obesity</td>
<td>11%</td>
<td>26%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Lee YS et al. DDW 2012; abstract 1054.
Effect of Metformin on HCC

- Taiwanese cohort study: National Health Insurance data (n=480,984)

Effect of Statins on HCC

- Meta-analysis of 6 observational studies ‘all comers’: with and without liver disease 3 Case-control and 3 Cohort studies


RR = 0.58 (95% CI 0.46–0.74). 42% Risk Reduction
### ADRESS-HCC Model

- **Scoring system to predict HCC incidence > 1.5% per year**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>Example</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (per year)</strong></td>
<td>1</td>
<td>Age</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>4</td>
<td>Diabetes</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><strong>Non-Caucasian Race</strong></td>
<td>4</td>
<td>Non-Caucasian</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Alcohol/Metabolic*</td>
<td>7</td>
<td>- Alcohol</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>- Viral</td>
<td>23</td>
<td>- HBV</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td><strong>Male Sex</strong></td>
<td>10</td>
<td>Male</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td><strong>Severity (CTP Score)</strong></td>
<td>2</td>
<td>CTP Score</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td><strong>Cut-off</strong></td>
<td>88</td>
<td>Score</td>
<td>71</td>
<td>115</td>
</tr>
</tbody>
</table>

*Metabolic: NASH, HH, A1ATD, Cryptogenic

Flemming JA et al. AASLD 2013
Validation of ADDRESS-HCC

- HALT-C Data
- Threshold for Screening: Sensitivity = 96%

Yang JD et al. AASLD 2013
The global HCC BRIDGE study (“Bridge to Better Outcomes in HCC”) is the first multiregional, large-scale, observational study to document real-world HCC patient experience from diagnosis to death\(^1\)

- Designed to provide additional understanding of global patterns of HCC therapy and associated outcomes across real-world clinical practice, as recorded in patient charts
- Aims to include all patients who have received treatment for HCC, regardless of treatment type
- Includes patients treated for HCC in 3 major regions: Asia, Europe, and North America
- Interim analysis examining the Asian cohort compared with the European and North American cohorts, based on available data as of March 2012

Kudo et al., APPLE 2012

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Median Survival from First Treatment

- Median follow-up time was approximately 24 months for this cohort
- Median OS was not reached for Taiwan and Japan
- Median OS was 35 mo for North America, 28 mo for South Korea, 21 mo for Europe, and 19 mo for China
What’s changed since 2005 > 2010 in the AASLD Guidelines?

- HCC surveillance in at risk patients is recommended every 6 months instead of every 6-12 months
  - AFP has been removed as a first line test for surveillance
- Sorafenib is recommended as first line option in patients who can not benefit from resection, transplantation, ablation or transarterial chemoembolization, and still have preserved liver function. (level 1)
- Radioembolization with Yttrium90-labeled glass beads has been shown to induce extensive tumor necrosis with acceptable safety profile. However, there are no studies demonstrating an impact on survival ... it cannot be recommended as standard therapy for HCC (level 2)
Proposal for changes 2013

- Add back laboratory tests such as AFP as a biomarker

- Consider AFPL3% and DCP which are both FDA approved as “risk markers” and not intended for diagnosis
Surveillance for Hepatocellular Carcinoma Biomarkers: AFP, AFP-L3 and DCP

Pattern of biomarkers in patients with HCC

HCC Biomarker Panel

- ALPL3% and DCP: FDA approved as risk markers
  - Near term predictor of developing HCC if no tumor is present on imaging

Uses and Utilization

- Higher levels associated with
  - Vascular invasion
  - More poorly differentiated tumors
  - Higher risk of recurrence after surgery and transplant
Guidelines For HCC Surveillance

<table>
<thead>
<tr>
<th></th>
<th>USA AASLD</th>
<th>Europe EASL</th>
<th>Japan JSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated</td>
<td>2010</td>
<td>2012</td>
<td>2009 (updating in 2013)</td>
</tr>
<tr>
<td>Interval</td>
<td>6 months</td>
<td>6 months</td>
<td>3-4 months for very high risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 months for high risk (3-4 months after treatment, 2013)</td>
</tr>
<tr>
<td>Test</td>
<td>Ultrasound</td>
<td>Ultrasound</td>
<td>Ultrasound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AFP, AFP-L3, DCP</td>
</tr>
</tbody>
</table>

More than one biomarker is recommended for HCC surveillance in Japan.
The biomarkers have been already approved in almost every regions.
Embrace and advised ultrasound protocols

- Protocol on how Ultrasounds are to be performed
- Requirements on who is trained and authorized to perform US studies
- Reporting /Synoptic guidelines
Proposed Liver Ultrasound Algorithm

Liver Dedicated Surveillance
Ultrasound (US) + HCC biomarkers in at risk patients*

- Poor/Fair quality US or abnormal biomarkers
  → #Eovist MRI (Or dynamic CT)

- Good/Excellent quality US and normal HCC biomarkers
  → US surveillance q6 months with biomarkers

- Negative MR
  → Abnormal US or increasing biomarkers

*AASLD Guidelines 2009

α blood tests AFPL3%/DCP (HCC serum biomarkers)
LI-RADS categorizes observations reflecting likelihood of benignity or HCC in at-risk patients, as shown in algorithm. Definitely or probably benign observations are categorized LR1 and LR2, respectively. Remaining observations that are not masses then are categorized LR3.

Masses with features suggestive of non-HCC malignancy are categorized Other Malignancy (OM). Remaining masses with definite tumor in vein are categorized LR5V.

Masses without definite tumor in vein are categorized LR3, LR4, or LR5 as shown in Table based on major features.

LR4 observations are designated A (diameter < 20mm) or B (diameter ≥ 20mm).

LR5 observations are designated A (diameter 10-19mm) or B (diameter ≥ 20mm).

Smaller observations must satisfy stricter criteria to be assigned an equivalent LR category.

The final category may be adjusted using ancillary features and then tie-breaking rules.

LR5A or 5B observations or biopsy-proven HCC lesions that have undergone loco-regional treatment are categorized LR5 Treated.

Click on the following links for details on LI-RADS: Reporting, Management, Technical Requirements.

Feedback? Email nrdr@acr.org
LiRADS 5 lesion: what is next?

- **Stage 0**
  - PS 0, Child-Pugh A
  - Very early stage (0)
    - Single < 2 cm
  - Early stage (A)
    - Single or 3 nodules < 3 cm, PS 0

- **Stage A - C**
  - PS 0-2, Child-Pugh A-B
  - Intermediate stage (B)
    - Multinodular, PS 0
  - Advanced stage (C)
    - Portal invasion, N1,M1, PS 1-2

- **Stage D**
  - PS > 2, Child-Pugh C
  - Terminal stage (D)
    - 3 nodules ≤ 3 cm

- **Resection**, **Liver Transplantation**, **RFA**, **TACE**, **Sorafenib**
  - Curative treatments
  - Palliative treatments

- **Symptomatic treatment**
Barcelona Clinic Liver Cancer (BCLC) Staging Classification and Treatment Schedule:
proposed modifications/additions*

Hepatocellular carcinoma

Stage 0
PST 0,
Child-Turcotte-Pugh A

Very early stage (0)
Single <2 cm carcinoma in situ
Ablation for cure

Increased portal pressure and elevated bilirubin levels

No
Resection
Liver transplantation (CLT or LDLT)

Single
Ablation for cure

Early stage (A)
Single nodule <5 cm or 3 nodules ≤3 cm, PST 0

Intermediate stage (B)
Multinodular, PST 0

Stage A-C
PST 0-2,
Child-Turcotte-Pugh A or B

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

Terminal stage (D)
PST >2,
Child-Turcotte-Pugh C

Supportive Care
Survival <3 months

Recovery

Liver transplantation (CLT or LDLT)

RFA (PEI) Ablation
(SBRT, RF, MWA, TABE > TARE, TACE)
• ≤ 3 tumors
• ≤ 5 cm

TAE or TACE
Local Chemo- or Radiotherapy
(Chemo or Bead embolization, Radioembolization)

Yes
Associated diseases

Yes
Sorafenib
Chemo

No

No
Salvage

Salvage

Median survival 11-20 months

Supportive Care
Survival <3 months

a Rarely used. b Confirmation required from RCTs.
Add tumor biopsy to the guidelines?
New Role for Biopsy

- Molecular profiling for prognosis and therapeutic decision making in HCC patients
  - DNA Microarray technique
  - miRNA profiling

Tissue MET as a Prognostic Factor

Median OS | Patients | Events
---|---|---
MET Dx Low | 9.0 | 13 | 9
MET Dx High | 3.8 | 15 | 15

HR: 2.94 (95% CI: 1.16-7.43) Log Rank: P=0.02

Trends in Liver Transplants in US

- HCV
- HCC
- Alcohol
- Cholestatic
- FHF
- Metabolic
Incident HCC on Transplant Waitlist

- UNOS data (2002-2011)
  - Incidence of de novo HCC on UNOS waitlist
  - 1,960 new HCCs in 34,932 waitlist registrants

- HCV 66%
- HBV 4%
- Alcohol 13%
- NASH / Cryptogenic 11%
- AIH 2%
- PBC 2%
- PSC 1%
- HH/A1AT 2%
- HH/A1AT 1%

Flemming JA et al. AASLD 2013.
**MELD Inflation**

- **Patients with HCC exceptions**
  - Start at 22 MELD points independent of your biologic MELD
  - Every three months additional points are added
  - Window of opportunity for successful transplant is wide

- **Patients without MELD exceptions**
  - MELD score based solely on your lab work
  - Patients with high MELD scores are often unstable
  - Window of opportunity to successfully undergo transplant is very narrow

<table>
<thead>
<tr>
<th></th>
<th>Bilirubin</th>
<th>INR</th>
<th>Creatinine</th>
<th>Biologic MELD</th>
<th>MELD exception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient A</td>
<td>2.5</td>
<td>2.7</td>
<td>1.1</td>
<td>22</td>
<td>none</td>
</tr>
<tr>
<td>Patient B</td>
<td>8</td>
<td>2.7</td>
<td>2.3</td>
<td>33</td>
<td>none</td>
</tr>
<tr>
<td>Patient C</td>
<td>1.0</td>
<td>0.9</td>
<td>0.8</td>
<td>6</td>
<td>33 (HCC)</td>
</tr>
</tbody>
</table>
AASLD Recommendations for HCC Surveillance are expected to change

**HBV carriers**
(Cost effective if risk >0.2%/y)
- Asian M≥40y, F≥50y
- Africans/Af Am >20yo
- Family history of HCC
- Cirrhosis

**Non HBV-cirrhosis**
- HCV
(Cost effective if risk >1.5%/y)
- Alcoholic cirrhosis
- Genetic hemochromatosis
- Primary biliary cirrhosis

**Increased risk but insufficient data to recommend surveillance**
- Alpha1-antitrypsin with cirrhosis?
- Non-alcoholic steatohepatitis with cirrhosis
- Autoimmune hepatitis with cirrhosis?
- **F3 disease?**

American Perspectives for HCC Management, Control and Prevention

Prevention
- Continued prevention of acute viral hepatitis infection
- Screen (Birth Cohort) for chronic HCV and HBV and link to treatment
- Improve treatment outcome/SVR rates
- Obesity epidemic? Behaviour modification
- Chemoprevention: Metformin? Statins?
- HBV Vaccine

Control
HCC surveillance strategies and linkage to care

Treatment
Thank you to

- APASL and the HSP for hosting this meeting
- Ray Kim for his HCC insights, leadership and slides
- Lewis Roberts for his research and teaching in biomarkers and genomics
- My North American Colleagues who have help shape HCC on our continent
  - Morris Sherman
  - Heshem El-Serag
  - Richard Finn
  - Ghassan Abou-Alfa
  - Adrian Di Besceglie