Update on Hepatocellular carcinoma: pearls for primary care management

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Objectives

• Pathogenesis of HCC
• New trends in epidemiology and surveillance
• Radiological assessment
• Resection and transplantation
Objectives

• Locoregional treatment
• Immunotherapy and systemic therapies
• HCC in the COVID-19 pandemic
Pathogenesis of HCC

- Next generation sequencing and identification signaling pathways
- Clinical and pathological features defining HCC sub-groups
- Role of microbiota on HCC development.
Epidemiology and surveillance

- Sixth most common diagnosed cancer worldwide
- Fourth leading cause of death in the world
- Most cases occur in chronic liver disease, cirrhosis main risk factor
- Incidence expected to increase
  - Population growth
  - Aging
<table>
<thead>
<tr>
<th>Hombres / Males (N = 14,848)</th>
<th>%</th>
<th>Mujeres / Females (N =11,694)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Próstata/Prostate</td>
<td>16.9</td>
<td>Mama/Breast</td>
<td>18.4</td>
</tr>
<tr>
<td>Pulmón y bronquios/Lung and bronchus</td>
<td>13.5</td>
<td>Colon y recto/Colon and rectum</td>
<td>13.4</td>
</tr>
<tr>
<td>Colon y recto/Colon and rectum</td>
<td>13.0</td>
<td>Pulmón y bronquios/Lung and bronchus</td>
<td>9.6</td>
</tr>
<tr>
<td>Hígado y ducto biliar/Liver and bile duct</td>
<td>6.7</td>
<td>Páncreas/Pancreas</td>
<td>6.0</td>
</tr>
<tr>
<td>Páncreas/Pancreas</td>
<td>5.0</td>
<td>Hígado y ducto biliar/Liver and bile duct</td>
<td>4.6</td>
</tr>
<tr>
<td>Estómago/Stomach</td>
<td>4.3</td>
<td>Cuerpo del útero, NOS/Corpus and uterus, NOS</td>
<td>4.4</td>
</tr>
<tr>
<td>Leucemia/Leukemia</td>
<td>3.3</td>
<td>Ovario/Ovary</td>
<td>4.4</td>
</tr>
<tr>
<td>Cavidad oral y faringe/Oral cavity and pharynx</td>
<td>3.2</td>
<td>Estómago/Stomach</td>
<td>3.8</td>
</tr>
<tr>
<td>Linfoma no-Hodgkin/Non-Hodgkin Lymphoma</td>
<td>3.1</td>
<td>Leucemia/Leukemia</td>
<td>3.3</td>
</tr>
<tr>
<td>Esófago/Eosophagus</td>
<td>3.1</td>
<td>Linfoma no-Hodgkin/Non-Hodgkin Lymphoma</td>
<td>2.8</td>
</tr>
<tr>
<td>Otros sitios primarios/Other sites</td>
<td>27.9</td>
<td>Otros sitios primarios/Other sites</td>
<td>29.5</td>
</tr>
</tbody>
</table>

Fuente de Datos: Archivo de Mortalidad provisto por el Registro Demográfico de Puerto Rico, octubre de 2016.
(Data Source: Mortality Case File provided by the Demographic Registry of Puerto Rico, October, 2016.)
Groups that will benefit from screening and surveillance

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Threshold Incidence for Efficacy of Surveillance (&gt;0.25 LYG; % per year)</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surveillance benefit</strong></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><strong>Surveillance benefit uncertain</strong></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.
HCC screening and surveillance

- Abdominal US with or without AFP very 6 months
- Low sensitivity on early stages
- Surveillance effectiveness on cohorts (NASH, post SVR HCC)
Diagnostic algorithm for a liver nodule

Liver nodule in cirrhosis detected on ultrasonography

1. Radiologic hallmarks on contrast-enhanced CT or MRI
   - Hyperenhancement in arterial phase and washout in portal venous phase
   - YES → Hepatocellular carcinoma
   - NO → Repeat ultrasound examinations every 3–4 months

2. Repeat ultrasound examinations every 3–4 months
   - Growing
   - YES → Biopsy
   - NO → Stable
     - Consider rebiopsy
     - Inconclusive
     - Conclusive, but no hepatocellular carcinoma

3. Radiologic hallmarks on the other imaging technique CT or MRI
   - YES → Hepatocellular carcinoma
   - NO → Biopsy
Figure 94-2. Dynamic computed tomography scan of a patient with hepatocellular carcinoma showing no lesion in the noncontrast phase, an enhancing lesion in the arterial phase of contrast administration, and a faint lesion in the portal venous phase seen better in the delayed phase.
CT/MRI LI-RADS® v2018 CORE

Untreated observation without pathologic proof in patient at high risk for HCC

- If cannot be categorized due to image degradation or omission → LR-NC
- If definite tumor in vein (TIV) → LR-TIV
- If definitely benign → LR-1
- If probably benign → LR-2
- If probably or definitely malignant but not HCC specific (e.g., if targetoid) → LR-M

Otherwise, use CT/MRI diagnostic table below

- If intermediate probability of malignancy → LR-3
- If probably HCC → LR-4
- If definitely HCC → LR-5
Treatment for HCC

- Resection
- Liver Transplant
- Locoregional therapies
- Systemic or targeted directed therapies
Liver transplant is the best treatment for HCC that is confined to the liver.
Resection

- 10 year recurrence free survival 22-25%
- In selected patients benefits over systemic therapy and locoregional therapy alone
- Perioperative mortality 5%
- Liver decompensation beyond 3 months 10-12%
Liver Transplant

- 10 year recurrence free survival 50-70%
- BCLC system
- Milan criteria for selection
  - Solitary <5 cm or up to 3 nodules each 3 cm
  - No macrovascular invasion or distant disease
Liver Transplant

- “Exception points”
- Mandatory 6 month waiting period
- Regional mean MELD at transplant
- Down-staging of lesion beyond Milan criteria has acceptable outcomes
Locoregional therapies

- Transarterial chemoembolization (TACE)
  - Most widely use intervention for intermediate stage
  - Median survival exceeds 40 months in selected cases
  - Considered palliative treatment

- Transarterial radioembolization (TARE)
  - Safe in patients with microvascular invasion
  - Cost!!
7.9x 7.6 cm lesion with arterial enhancement and washout at right hepatic lobe
Follow up image after TACE where a 3x2.3cm lesion is observed on segment VII consistent with partial response.
## Immunotherapies and systemic therapies

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Line of therapy</th>
<th>Active agent</th>
<th>Control</th>
<th>Primary end-point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHARP</td>
<td>First-line</td>
<td>Sorafenib</td>
<td>Placebo</td>
<td>OS</td>
<td>10.7 vs 7.9 HR 0.69 (95% CI 0.55-0.87)</td>
</tr>
<tr>
<td>REFLECT</td>
<td>First-line</td>
<td>Levatinib</td>
<td>Sorafenib</td>
<td>OS</td>
<td>13.6 vs 12.3 HR 0.92 (95% CI 0.79-1.06)</td>
</tr>
<tr>
<td>RESORCE</td>
<td>Second-line</td>
<td>Regorafenib</td>
<td>Placebo</td>
<td>OS</td>
<td>10.6 vs 7.8 HR 0.63 (95% CI 0.50-0.79)</td>
</tr>
<tr>
<td>CELESTIAL</td>
<td>Second- and third-line</td>
<td>Cabozantinib</td>
<td>Placebo</td>
<td>OS</td>
<td>10.2 vs 8.0 HR 0.76 (95% CI 0.63-0.92)</td>
</tr>
<tr>
<td>REACH-2</td>
<td>Second-line and AFP&gt;400 ng/mL</td>
<td>Ramucirumab</td>
<td>Placebo</td>
<td>OS</td>
<td>8.5 vs 7.3 HR 0.71 (95% CI 0.531-0.949)</td>
</tr>
<tr>
<td>Checkmate-440</td>
<td>Second-line</td>
<td>Nivolumab</td>
<td>None</td>
<td>ORR, OS, safety</td>
<td>17%, 15.0</td>
</tr>
<tr>
<td>KEYNOTE-224</td>
<td>Second-line</td>
<td>Pembrolizumab</td>
<td>None</td>
<td>ORR, OS, safety</td>
<td>17%, 12.9</td>
</tr>
<tr>
<td>KEYNOTE-240</td>
<td>Second-line</td>
<td>Pembrolizumab</td>
<td>Placebo</td>
<td>PFS, OS</td>
<td>PFS 3.0 vs 2.8 HR 0.718 (95% CI 0.570-0.904) OS 13.9 vs 10.6 HR 0.781 (95% CI 0.611-0.998)</td>
</tr>
<tr>
<td>Checkmate-459</td>
<td>First-line</td>
<td>Nivolumab</td>
<td>Sorafenib</td>
<td>OS</td>
<td>16.4 vs 14.7 HR 0.85 (95% CI 0.72-1.02)</td>
</tr>
<tr>
<td>IMbrave150</td>
<td>First-line</td>
<td>Atezolizumab + bevacizumab</td>
<td>Sorafenib</td>
<td>OS% 12 mo., PFS</td>
<td>PFS 6.8 vs 4.8 HR 0.59 (95% CI 0.47-0.76) OS 67.2% vs 54.6% (95% CI 45.2-64.0)</td>
</tr>
</tbody>
</table>
HCC and SARS-CoV-2

- Not available data that HCC as risk factor increase mortality of SARS-CoV-2
- Worse outcomes of COVID-19 on patient with non-hepatic types of cancer
- Fewer patients presented to Tumor Boards
- More than 21% patient experience delays in treatment of more than 1 month
- COVID-19 infection more common cause of delay of treatment on 2019
Questions?