Overview of Liver Cancer

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Liver cancer is difficult to treat, and lethal if not caught early. But its most common causes, such as hepatitis viruses and obesity, can be prevented.
Liver
The liver contributes to a wide range of functions, including digestion, detoxification and metabolism. It is also the only internal human organ that can regenerate: as little as 25% of its original tissue is necessary to restore the liver to its original size. HCC is named after the cells in which it develops, the hepatocytes.

Gall bladder
Bile acids, which are used in digestion, are stored in the gall bladder and released into the small intestine on ingestion of fatty foods. Certain bacteria in the gut convert bile acids into toxic chemicals that might contribute to liver cancer.

Bile duct
Bile, which is produced in the liver, travels to the gall bladder and then on to the small intestine through the thin, tubular bile duct. Bile-duct cancer, also known as cholangiocarcinoma, is less common than disease that starts in the lobes of the liver itself.

HCC
HCC accounts for the overwhelming majority of liver cancers. It is the disease addressed by this Outlook, as well as by most liver-cancer research.

Bile-duct cancer
Bile-duct cancer is more common than HCC in some Asian countries, but it makes up a relatively small number of liver-cancer cases worldwide.

Hepatoblastoma and various liver sarcomas and carcinomas
These include most cases of paediatric liver cancer, which has increased in incidence in recent years but is still a rare disease.
Age-standardized liver-cancer rates per 100,000 people

- >9.2
- 5.4–9.2
- 4.2–5.4
- 3.0–4.2
- <3.0
- No data

1. UNITED STATES
   Poor diet, low activity levels and genetics all contribute to high rates of obesity and fatty liver disease in the United States. Liver cancer is 17–18% likelier among overweight people and 83–89% likelier among obese people.

2. GAMBIA
   The hepatitis B virus (HBV) causes around half of all cases of liver cancer worldwide. Gambia once had one of the world’s highest rates of HBV infection, but a vaccination programme started in 1990 has begun to have an effect.

3. EGYPT
   The hepatitis C virus (HCV) is responsible for about 15% of all global liver-cancer cases, and Egypt has the world’s highest rate of HCV.

4. SUDAN
   Aflatoxin fungi, found on crops such as maize (corn) and peanuts, might cause up to 28% of liver cancers worldwide. Sudan has unusually high crop concentrations of aflatoxin, which has synergistic effects with HBV and HCV.

5. MONGOLIA
   Mongolia has the world’s highest incidence of liver cancer, at 78 cases per 100,000 residents. It has unusually high rates of alcohol abuse and infection with HBV and HCV.

6. THAILAND
   Eating raw fish infested with a parasitic flatworm called a liver fluke can cause bile-duct cancer. The liver fluke is common in Thailand, one of the few countries where bile-duct cancers are more common than HCC.

- 2009: First year since 1969 that HCC rates in the United States did not rise
- 95: Percentage of adults in Gambia who have been exposed to HBV (upper estimate)
- 14.7: Percentage of people in Egypt who are infected with HCV
- 60: Percentage of liver-cancer cases in Sudan (before the country split) that could be due to aflatoxin
- ×8: Difference between liver-cancer incidence in Mongolia and the global average
- 89: Percentage of liver-cancer cases caused by liver flukes in Khon Kaen, Thailand
HCC may be prevented.
Breakthrough in the Understanding of Liver Cancer in 2013 to 2014
A link of liver cancer to bacteria living in the gut

**BACTERIAL LINKS**

The gut and liver are intimately connected. Bacterial populations living in the gut change their composition in response to diet, and such bacterial activity might contribute to liver-cancer risk and progression.

1. **FATTY FOOD**
   - The liver produces digestive chemicals called primary bile acids. These are stored in the gall bladder and then released into the intestines during a meal.

2. **Hepatic portal vein**
   - Nutrients, bile acids and bacterial by-products, including LPS and DCA, pass into the liver.

3. **Intestine**
   - When exposed to a high-fat diet, populations of Firmicutes bacteria rise. Many of these bacteria produce LPS, and some of them convert primary bile acids to secondary bile acids, including the toxic DCA.

4. **Chromically high levels of DCA and LPS can increase cancer risk.**
   - LPS binds to immune receptors called TLRs, leading to inflammation in the liver.

5. **DCA causes DNA damage in the liver**

*Firmicutes bacteria* Other phyla of bacteria

DCA, deoxycholic acid; LPS, lipopolysaccharide; TLR, Toll-like receptor.
Trans-ancestry mutational landscape of hepatocellular carcinoma genomes  

Whole-genome sequencing identifies recurrent mutations in hepatocellular carcinoma  
Zhengyan Kan et al., Genome Research www.genome.org 23:1422–1433 2013,
Advancement in the Clinical Treatment of Liver Cancer
HCC Diagnosis

Algorithm for investigation of small nodules found during surveillance

- **Nodule**
  - < 1 cm
    - Repeat US at 3 months
      - Growing / changing character
        - Investigate according to size
      - Stable
  - ≥ 1 cm
    - 4 phase multidetector CT / dynamic contrast enhanced MRI
      - Arterial hypervascularity AND venous or delayed phase washout
        - Yes
          - Arterial hypervascularity AND venous or delayed phase washout
            - Yes
              - HCC
            - No
        - No
          - Biopsy
          - Other contrast enhanced study

BCLC Staging and Treatment

Stage 0
PST 0, Child-Pugh A

Very early stage (0)
1 HCC nodule < 2 cm
Carcinoma in situ

1 HCC nodule < 2 cm
Portal pressure/ bilirubin
Increased
Normal
Resection
Liver transplantation
Curative treatments

Early stage (A)
Up to 3 HCC nodules < 3 cm, PST

Up to 3 nodules ≤ 3 cm
Associated diseases
No
Yes
RFA

Intermediate stage (B)
Multinodular, PST 0

Stage A–C
PST 0–2, Child-Pugh A–B

Stage D
PST > 2, Child-Pugh C

Advanced stage (C)
Portal invasion, N1, M1, PST

End stage (D)

TACE
Sorafenib
Palliative treatments
Symptomatic treatment

# HCC Treatment Levels of Evidence

<table>
<thead>
<tr>
<th>Treatments Assessed</th>
<th>Benefit</th>
<th>Evidence</th>
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</thead>
<tbody>
<tr>
<td><strong>Surgical treatments</strong></td>
<td></td>
<td></td>
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<tr>
<td>Surgical resection</td>
<td>Increased survival</td>
<td>3iiA</td>
</tr>
<tr>
<td>Adjuvant therapies</td>
<td>Uncertain</td>
<td>1iiA</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>Increased survival</td>
<td>3iiA</td>
</tr>
<tr>
<td>Neoadjuvant therapies</td>
<td>Treatment response</td>
<td>2iiDiii</td>
</tr>
<tr>
<td><strong>Locoregional treatments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous treatments</td>
<td>Increased survival</td>
<td>3iiA</td>
</tr>
<tr>
<td>PEI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>Better local control</td>
<td>1iiD</td>
</tr>
<tr>
<td>Chemoembolization</td>
<td>Increased survival</td>
<td>1iiA</td>
</tr>
<tr>
<td>Arterial chemotherapy</td>
<td>Treatment response</td>
<td>3iiDiii</td>
</tr>
<tr>
<td>Internal radiation (Y90, I131)</td>
<td>Treatment response</td>
<td>3iiDiii</td>
</tr>
<tr>
<td><strong>Systemic treatments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Increased survival</td>
<td>1iA</td>
</tr>
<tr>
<td>Tamoxifen, Chemotherapy, IFN</td>
<td>No benefit</td>
<td>1iA-1iiA</td>
</tr>
</tbody>
</table>

Classification of evidence adapted from National Cancer Institute:

**Study design:**
- Randomized controlled trial, meta-analysis = 1
  - Double-blinded: 1i, nonblinded: 1ii
- Nonrandomized controlled trials = 2
- Case series = 3
  - Population-based 3i, non-population-based, consecutive 3ii, non-population-based, nonconsecutive: 3iii

**Endpoint:**
- Survival (A)
- Cause-specific mortality (B)
- Quality of life (C)
- Indirect surrogates (D)
  - Disease-free survival [Di]
  - Progression-free survival [Dii]
  - Tumor response [Diii]

Evolving Role of Y90

Unresectable Solitary Hepatocellular Carcinoma Not Amenable to Radiofrequency Ablation: Multicenter Radiology-Pathology Correlation and Survival of Radiation Segmentectomy. Riad Salem et al., Hepatology July 2014

Radiation lobectomy: Time-depdendent analysis for future liver remnant volume in unresectable liver cancer as a brdge to resection. Riad Salem et al., Journal of Hepatology 2013
Try and try again to find systemic therapy for HCC
<table>
<thead>
<tr>
<th>1st Line (phase II), NCT01761266</th>
<th>Lenvatinib (E7080)</th>
<th>VEGFR1-3, FGFR1-4, RET, KIT and PDGFRβ</th>
<th>Sorafenib</th>
<th>2015</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Line</td>
<td>Sunitinib Pfizer</td>
<td>Sorafenib</td>
<td>2013</td>
<td>negative</td>
<td></td>
<td></td>
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<tr>
<td>1st line (n=577) JCO.2012.47.3009</td>
<td>Brivanib BRISK-FL Study</td>
<td>VEGFR, FGFR</td>
<td>Sorafenib</td>
<td>2013</td>
<td>9.9 months vs. 9.5 months</td>
<td>TTP, ORR DCR similar</td>
</tr>
<tr>
<td>Adjuvant phase III J Clin Oncol 32:5s, 2014 n=1114</td>
<td>Sorafenib (STORM) Bayer-Onyx</td>
<td>Placebo</td>
<td>2014</td>
<td>OS, HR0.995 (0.761 – 1.300) p=0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Line (phase III) NCT02029157</td>
<td>Tivantinib c-MET inhibitor;</td>
<td>Placebo</td>
<td>2016</td>
<td>High c-met level</td>
<td></td>
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</tr>
<tr>
<td>2nd line (phase III) (n=565)</td>
<td>Ramucirumab (REACH) Lilly</td>
<td>VEGFR-2</td>
<td>Placebo</td>
<td>2014</td>
<td>OS HR 0.866 (p=0.1391) 9.2 months vs. 7.6 months</td>
<td>TTP (3.48 vs. 2.63 months) (p=0.0001) OR 7.1% vs. 0.7% (p&lt;0.0001)</td>
</tr>
<tr>
<td>2nd line (phase III) ESMO Congress 2014 LBA17 N=202</td>
<td>Axitinib VEGF receptors 1-3</td>
<td>Placebo</td>
<td>2014</td>
<td>12.7 months vs. 9.7 months (HR 0.870, p=0.211)</td>
<td>PFS 3.6 months vs. 1.9 months (HR 0.618; p=0.004)</td>
<td></td>
</tr>
<tr>
<td>J Clin Oncol 32, 2014 (suppl 3; abstr 172) (n=546)</td>
<td>Everolimus (EVOVLE-1) Novatis</td>
<td>mTOR</td>
<td>Placebo</td>
<td>2014</td>
<td>7.56 vs. 7.33 months (HR 1.05, p=0.675)</td>
<td>TTP 2.96 vs. 2.47 months (HR 0.55, p=0.04) DCR 56.1% vs. 45.1% (p=0.014)</td>
</tr>
</tbody>
</table>
Summary

1. Liver cancer also causes a disproportionate number of cancer-related deaths.

2. Liver disease takes decades to progress to cancer, which makes prevention research difficult.

3. Surveillance for early diagnosis and treatment is the key.

4. For a patient with a newly diagnosed liver cancer, a multidisciplinary team should be involved in developing the treatment plan.