2023 ACG / FGS ANNUAL SPRING SYMPOSIUM
MARCH 10-12, 2023 | HYATT REGENCY COCONUT POINT
NAPLES, FLORIDA
Register online: meetings.gi.org

ACG 2023
OCTOBER 20-25, 2023
VANCOUVER, CANADA

Save the Date!
Be sure your passport is up to date!
Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2023 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2024 for this activity.
MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 7 – Thursday, February 16, 2023
Post-COVID-19 Disorders of Gut-Brain Interaction/Functional Gastrointestinal Disorders
Faculty: Max L. Schmulson, MD
Moderator: Sarah K. McGill, MD, MSc, FACG
At Noon and 8pm Eastern

Week 8 – Thursday, February 23, 2023
3rd Space Endoscopy
Faculty: Gregory B. Haber, MD
At Noon and 8pm Eastern

Visit gi.org/ACGVGR to Register
Disclosures

Ayse Aytaman, MD, FACP
Exact Sciences: Research Grant

Janice Jou, MD
Gilead: Research Grant

*All of the relevant financial relationships listed for these individuals have been mitigated
Liver Cancer Update and Review for the Gastroenterologist

Ayse Aytaman, MD, FACP
Chief of Gastroenterology and Hepatology
VA New York Harbor HCS Brooklyn
Clinical Professor of Medicine SUNY Downstate College of Medicine
Director VISN 2 Liver Team and Liver Tumor Board

Educational Objectives

• Understand changes in epidemiology,
• Review available data on prevention
• Appreciate changes on surveillance considering challenging populations
• Go over the diagnostic challenges and role of imaging and liver biopsy
• Evaluate the staging of HCC
• Understand rapidly changing treatment landscape with an overview of curative and palliative options
• Review role of liver transplantation basics for HCC
• Role of palliative care, end of life care, frailty
• Impact of multidisciplinary teams, dedicated tumor boards and population health management
Why is HCC so challenging?

HCC is unique among cancers:

• 1 patient, 2 diseases
  Cirrhosis leads to
  • multifocal liver cancer
  • high recurrence rates

• Cirrhosis complicates treatment and trial design

• HCC can be diagnosed by imaging alone

• HCC is the only solid organ malignancy for which transplant offers cure

Epidemiology

Changing trends
HCC: GLOBAL HEALTH CHALLENGE

- 3rd leading cause of cancer-related death worldwide
- Growing incidence worldwide.
- Estimates: >1 million affected individuals by 2025.
- Most common form of liver cancer (>90%).
- Most prominent risk factors for HCC:
  - HBV in most parts of Asia, Mongolia
  - HCV in Western Europe, North America, Japan
  - ETOH in Central and Eastern Europe
- Non-alcoholic steatohepatitis (NASH) is becoming the fastest growing etiology of HCC, particularly in the West.
- Mutational signatures have established aristolochic acid and tobacco as potential pathogenetic cofactors.

Fastest Rising Cause of Cancer-Related Death in the US

Changes in cirrhosis/HCC epidemiology: Next 5-10 years

1. HCV-related cirrhosis/HCC will decline dramatically:
   - Deaths in aging baby boomers with HCV
   - Eradication of HCV with DAAs in unprecedented numbers
2. Patients with cured-HCV and cirrhosis make up a large % of cirrhosis
   - What is their HCC risk and optimal screening?
3. NAFLD-cirrhosis/HCC will continue to increase slowly but steadily
   - Overall risk lower but population attributable fraction high
   - Epidemics of obesity and diabetes and other factors
4. Overall cirrhosis prevalence and HCC incidence may decline...transiently
5. Eventually, if NAFLD-cirrhosis predictions are true, overall cirrhosis prevalence and HCC incidence will start increasing again

Prevention Before Surveillance

Vaccinate/Eradicate/Control Viral Hepatitis
Alcohol cessation
Control of Metabolic Syndrome/Insulin Resistance
Healthy lifestyle with exercise

Risk factors for HCC

RISK FACTORS FOR HCC
- Chronic hepatitis B
- Chronic hepatitis C
- Cirrhosis
  - Alcoholic
  - NASH
  - Autoimmune
  - Primary syphilis
  - Primary biliary cirrhosis
  - Wilson's disease
  - Alpha-1 antitrypsin deficiency
  - Hereditary hemochromatosis
- Aflatoxins
- Microcystins
- Diabetes
- Smoking

PREVENTION
- Prevent infection with HBV and HCV
- Prevent viral hepatitis
- Control metabolic syndrome
- Maintain healthy weight and active lifestyle
- Stop EtOH and smoking
- Control iron stores
- Avoid environmental toxins
- Consider chemoprotection as appropriate

AGE
STRONG MALE PREDOMINANCE
HISPANIC RACE
High incidence of PNPLA3 (NASH CIRRHOSIS)
SMOKING

Coffee reduces risk for HCC: an updated meta-analysis.

Caffeine is an antagonist of the A2a adenosinergic receptor expressed on activated hepatic stellate cells and other liver myofibroblasts:
- Reduction in liver metalloproteinase (MMP) secretion
- Anti-oxidant and anti-inflammatory

Improved enzymes,
Decreased risk of progression to cirrhosis
Lower mortality, lower rate of HCC
Improved responses to HCV Rx
Lower severity of steatohepatitis

2 or more cups a day associated with 45% reduction of HCC (0.38-0.53)

**Finnish smokers' study:**
RR of HCC per cup 0.82 (0.73-0.93)
CLD mortality 0.55 (0.48-0.63)

**NHANES:**
AST, ALT, ALkPhos & GGT all lower in coffee drinkers

Xiao Q, Setha R, Graubard BI. Hepatology 2013; Aug; 58: 2393-9
Saab S, Mallam D, Cox GA. Liver Int. 2014 Apr; 34 (4): 495-504

AASLD 2021
Prevention

**METFORMIN**

*Galega officinalis*: Goat’s rue, French lilac, Italian fitch, professor weed

Metformin inhibits hepatocyte proliferation, induces cell cycle arrest at G0/G1 AMP-activated protein kinase

- 10 studies, 334K pts
- Metformin: OR HCC 0.50 (0.34-0.73)
- Sulfonylurea 1.62
- Insulin 2.6
- TZDs 0.54 (0.28-1.02).

Each year of metformin use:
7% reduction RR of HCC in diabetic patients (OR=0.93, 0.91-0.94)

ASA

- NIH-AARP Diet and Health Study:
  RR of developing HCC = 0.59 (0.45-0.77)
- Reduces Fibrosis post transplant

**STATINS**

- Tsan: Clear dose response with HRs of
  - 0.66 (29-90d), 0.41 (90-365d) and 0.34 (>365d)
- Meta-analysis of 10 studies with 1.6 million pts:
  - OR of HCC with statins/no statins 0.63 (0.52-0.76)


Effects of Metformin Exposure on Survival in a Large National Cohort of Patients With Diabetes and Cirrhosis

Metformin use is associated independently with reduced overall, but not liver-related, mortality, hepatocellular carcinoma, or decompensation after adjusting for concomitant statin and ACE inhibitor/angiotensin-2–receptor blocker exposure.

Effects of Hypercholesterolemia and Statin Exposure on Survival in a Large National Cohort of Patients With Cirrhosis:

VOCAL STUDY GROUP

Exposure to statin therapy was associated with an 8.0%–8.7% annual decrease of mortality.

In well-compensated cirrhosis:
Lower risk of hepatic decompensation
Decreased liver cancer incidence

Patients with advanced cirrhosis (CTP C) did not derive a survival benefit.

Prevention Key Take Aways

- Control of underlying liver disease
- Statins
- ASA
- Vitamin D
- Coffee
- Exercise
- Healthy diet
- Smoking cessation
- ? ACE/ARB
- ? Metformin (overall survival benefit)
Screening

AFP+ SONO remains the current standard
AASLD, EASL, APASL, USPSTF

HCC Surveillance

- All cirrhotics regardless of etiology
- HCV cirrhosis or HCV stage 3 fibrosis prior to HCV eradication
- HBV sAg positive patients from endemic areas:
  - Men over 40
  - Women over 50
  - Family history of HCC
  - Sub Saharan origin: starting in early 20ies

AASLD HCC Guidance 2018
Liver cancer surveillance saves lives

Surveillance for HCC remains controversial due to lack of randomized data

Articles from 2014-2020
Inclusion: Surveillance benefits and harms in patients with cirrhosis

Systematic review/Meta-analysis:
59 studies with 145,396 patients

HCC Surveillance associated with:

Early stage detection:
OR 1.86, 95%CI 1.73-1.98

Receipt of curative therapy:
OR 1.83, 95%CI 1.69-1.97

Overall survival:
HR 0.67, 95%CI 0.61-0.72

Surveillance harms:
4 studies with 2,578 patients

Occurred in 8.8%-27.5% of patients across studies
Most mild in severity
Lack of data on financial or psychological harms

Singal AG, et al. J Hepatol. 2022

Protein-, genome- and microbiota biomarkers currently in use or potential future use in the surveillance and diagnosis of HCC

GALAD SCORE had the best performance characteristics for early detection of HCC in patients with cirrhosis. Compared to AFP, AFP-L3, DCP alone, GALAD could prevent unnecessary MRI/CT in 54% of patients with cirrhosis. 82% of patients detected at very early or early stages of disease.

We have data on Viral and non-viral HCC, FDA approved, might have a role in NASH surveillance where obesity decreases the efficacy of imaging.

HCC risk calculated by our web-based models for selected patients in “low-risk”, “medium-risk” and “high-risk” categories

<table>
<thead>
<tr>
<th>Cirrhosis etiology</th>
<th>LOW-RISK PATIENTS 5-year HCC risk &lt;5%</th>
<th>MEDIUM-RISK PATIENTS 5-year HCC risk 5% to 15%</th>
<th>HIGH-RISK PATIENTS 5-year HCC risk &gt;15%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NAFLD</td>
<td>ALD</td>
<td>NAFLD</td>
</tr>
<tr>
<td>Age</td>
<td>61</td>
<td>67</td>
<td>62</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>BMI</td>
<td>31</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.2</td>
<td>4.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Serum AST</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Serum ALT</td>
<td>35</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>225</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td>Estimated 5-year HCC Risk</td>
<td>0.40%</td>
<td>2.6%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Models available at: [www.hccrisk.com](http://www.hccrisk.com)
Ioannou J Hepatol. 2018 Nov;69(5):1088-1098
The magnitude of HCC risk varies depending on the underlying etiology:
Being highest in patients with active HCV cirrhosis,
Lower in cured HCV
Lowest in those with NAFLD cirrhosis.

Alcohol drinking and overweight were associated with an increased HCC risk irrespective of underlying etiology.

New Challenges for HCC Screening

Patients with cirrhosis and cured HCV:
- Risk is reduced after SVR, but residual risk persists
- How does it change over time after SVR?
- Cost effectiveness of screening?

Patients with NAFLD-cirrhosis:
- Nearly one-fourth of NAFLD-related HCC occurs in the absence of cirrhosis
- Annual HCC incidence of 0.008 per 100 person-years
  - Very large population of NAFLD-cirrhosis predicted in next 5-10 years
  - Have lower HCC risk than HCV-cirrhosis \( \rightarrow \) lower cost-effectiveness
  - Older, more comorbidities \( \rightarrow \) reduced treatment options
  - Obesity: reduces the accuracy of ultrasound screening
- Risk stratification tools to identify those at highest risk
- Surveillance on a case-by-case basis
- Developing better screening tests is critical

Farhang Zangneh H et al. CGH 2019
Orci LA et al. CGH 2022
Diagnosis and Staging Challenges

Severity of the underlying liver disease influences staging and management options.

Liver Imaging Reporting and Data System (LI-RADS)

HCC is the only malignancy which can be diagnosed and treated by imaging only.

LI-RADS were developed by American College of Radiology 2011
Adapted by AASLD into AASLD/IDSA Guidance into HCC clinical practice guidance in 2018
Updated every 3-4 years, dynamic 2021 update by a steering committee with representatives from AASLD, UNOS, ACR
Improves communication between radiologist and hepatocellular carcinoma teams creating a standardized language
Now including CT, MRI with extracellular and hepatobiliary agents, ultrasound, contrast enhanced ultrasound, expansion under way for evaluation of benign liver lesions.

LI-RADS: assign a relative probability for HCC

https://www.ajronline.org/doi/full/10.2214/AJR.20.24272
When not to use LI-RADs

1) No risk factors for liver disease
2) Less than 18 years of age
3) Patients with cirrhosis due to congenital hepatic fibrosis
4) Cirrhosis due to vascular disorder (hereditary hemorrhagic telangiectasia, Budd-Chiari syndrome, chronic portal vein occlusion, cardiac congestion, or diffuse nodular regenerative hyperplasia)

LI-RADS should not be applied to path proven malignancies or path proven benign lesions

Patients with chronic hepatitis C virus infection or nonalcoholic steatohepatitis with advanced fibrosis creates an important knowledge gap warranting further research

LI-RAD Diagnostic Categories
Criteria for HCC Diagnosis

- Dynamic imaging required for diagnosis
  - Early arterial enhancement
  - Portal venous, delayed washout
  - Capsule formation

AASLD/LIRAD SURVEILLANCE AND DIAGNOSIS ALGORITHM 2018

CT/MRI Diagnostic Table

<table>
<thead>
<tr>
<th>Observation size (mm)</th>
<th>No APHE</th>
<th>APHE</th>
<th>APHE (pt. req)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>LR3</td>
<td>LR3</td>
<td>LR3</td>
</tr>
<tr>
<td>≥ 20</td>
<td>LR4</td>
<td>LR4</td>
<td>LR4</td>
</tr>
<tr>
<td>Count major features:</td>
<td>None</td>
<td>CTE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤ 20</td>
<td>LR5</td>
<td>LR5</td>
</tr>
</tbody>
</table>

LIRADS-TIV (Tumor in vein): Cancer invading 1 or more veins

Marrero et al. Hepatology, Vol. 68, No. 2, 2018

https://sites.google.com/site/rlow53/HCC2.jpg
Factors Determining Prognosis

- **Tumor stage**
  - Size
  - Number
  - Location
  - Vascular invasion
  - Extrahepatic spread

- **Anatomy** is key to determining feasibility of resection

- **Liver function**
  - Principal driver of treatment decisions
  - Presence or absence of portal hypertension

- **Overall patient health/performance**
  - ECOG Performance score/Karnofsky score

Marrero JA et al. Hepatology, VOL. 68, NO. 2, 2018
BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update

Treatment basics
The treatment landscape (BCLC 0, A, B)

**Surgical Options**
- Liver resection
- Liver transplantation

**Locoregional Therapies**
- Ablation
  - Radiofrequency
  - Microwave
  - Cryoablation
  - Chemical (EtOH)
  - Irreversible electroporation
  - Histotripsy
  - SBRT?
- Transarterial
  - Chemoembolization (TACE)
  - TARE (90Yttrium microspheres)
  - SBRT

AASLD HCC GUIDANCE 2018

- **Resection is the treatment of choice**
  For localized HCC occurring in the absence of cirrhosis or
  Resectable HCC and in the setting of cirrhosis with intact liver
  function and absence of CSPH.

- **Transplantation is the treatment of choice** for patients with early-stage
  HCC occurring in the setting of CSPH and/or decompensated cirrhosis.
  Access is limited by the extreme organ shortage.
  With many curative options transplant in well compensated cirrhotic
  should be reserved for recurrence and/or decompensation.

  CSPH Clinically Significant Portal Hypertension
Evolving Policy in LT for HCC

LiRADS criteria for HCC Dx & stage

Rigorous HCC radiographic criteria to qualify for MELD exception points

Adopted 1/2014

Delay HCC MELD exception 6 months

“Ablate and wait” to identify and exclude aggressive HCC

Adopted 1/2016

Cap HCC MELD exception at 34

Cirrhotics with MELD ≥ 35 throughout region have priority over HCC patients –

Adopted 1/2016

Adopted 3/2017

New Rules for MELD Exception Effective 1/21/2016

- No MELD exception points are granted for 6 months from time of initial application for MELD exception
- Must be within Milan criteria (1 lesion <5cm or 3 lesions or less each less then 3cm) at time of initial application
- Repeat imaging every 3 months must demonstrate continued locoregional control
- Exception score awarded:

<table>
<thead>
<tr>
<th>TIME</th>
<th>Initial</th>
<th>Points:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>9 months</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>12+ months</td>
<td></td>
<td>34 (maximum)</td>
</tr>
</tbody>
</table>

Share 35 does not apply to HCC’s
Final changes: 12/2017

- Candidates within 150 mile circle of the donor hospital

TRANSPLANT IS BECOMING A LESS VIABLE OPTION ESPECIALLY FOR PATIENTS WITH ADEQUATE LIVER FUNCTION

For other MELD 15-31, organs will continue to be allocated within the donor service area according to MELD score
- Extended criteria livers from donation after cardiac death will continue to be allocated locally

Variables to Consider in Decision Resection vs Ablation for Early HCC

- Liver reserve: CPT score, MELD score
  - CSPH (Clinically significant pHTN)
  - Plts (>100 or not)
  - Albumin >3.5
  - INR<1.5
  - Bilirubin (normal or not)
  - HVPG (<10 or not)
- Location of the lesion, anatomic considerations
- Number of the lesions and lobes/segments involved
- Absence of metastasis and main PV and IVC tumor thrombus
- Absence/control of cardiopulmonary comorbidities
- Available expertise in each facility

Candidates for surgery:
- 5%-15% of HCC in Western countries but a higher percentage in Asia (HBV)
Liver Resection is Getting Less Invasive: Every Day We Are Pushing the Envelope Further

*DaVinci Robotic Partial hepatectomy*

New minimally invasive techniques are now pushing the envelope

Locoregional Therapy

Define upfront your goal with locoregional therapy:

1) **Curative**: Limited to very early tumors treated with RFA/MWA/?SBRT
2) **Bridge to liver transplantation (OLT)**
3) **Downstage to OLT/Resection**
4) **Palliative**: With goal to improve overall survival without the ability to cure

Talk upfront about systemic therapy: they’re eventually going to be going down the road to systemic therapy if they can preserve their liver function.

The decision which liver-directed therapy to start with is dependent on

- Patient and tumor characteristics
- Heavily dependent upon the experience of the center
Comparison of microwave ablation and hepatic resection for HCC: A meta-analysis

MWA may be superior to hepatic resection (HR) in select cases:
- As Effective as HR in terms of Overall survival (OS), Disease Free Survival (DFS), Recurrence Rates,
- Shorter Operation Time, Less amount of blood loss in operation,
- Fewer Complications

Technology is Improving Considerably

New-generation MWA may create a more predictable ablation zone and a larger ablation volume in a shorter time period.

Novel sono transducer for ablation probe guidance

Prof. Shuicho Shiina Juntendo Univ Tokyo

SBRT for HCC

• SBRT is an emerging treatment modality offering potentially curative local therapy for HCC.
• SBRT is applicable across BCLC stages (bridge to transplant, BCLC A,BCLC B, portal vein thrombosis) as an alternative treatment strategy to TACE/RFA, or in recurrent tumors as salvage therapy.
• The recent prospective and retrospective studies have shown the safety and efficacy of SBRT with 2-year local control ranging from 68-95%.
• Smaller randomized trials of external beam radiation therapy suggest high efficacy of radiation therapy compared to other treatments for patients with unresectable HCC, and phase III trials comparing SBRT with other modalities are ongoing.

Lewis S, Dawson L et al Review JHEP Reports 2022 vol. 4 j 100498
SBRT for Small HCC
Photons versus Protons

Protons should be considered for dome and central tumors
> 3 cm – maximal liver sparing,
potentially reduced radiation toxicity

Protons should also be considered for any tumor > 5 cm
if other ablative options fail to achieve adequate coverage

Gandhi, Pract Radiation Oncol, 2015

Location: Dome

Location: Central

Small Tumor:
No Difference

Gandhi, Pract Radiation Oncol, 2015
SBRT vs RFA?

Univ Michigan 2004 to 2012,
224 patients with inoperable, nonmetastatic HCC
RFA (n = 161) to 249 tumors or image-guided SBRT (n = 63) to 83 tumors
Freedom from local progression (FFLP) and toxicity were retrospectively analyzed.

1- and 2-year FFLP for tumors treated with:
- RFA: 83.6% and 80.2%
- SBRT: 97.4% and 83.8%


Expected overall survival of SBRT is nearly identical to RFA in HCCs smaller than 3 cm
SBRT may have an advantage for tumors 2 cm and larger

TACE (Transarterial Chemoembolization) vs DEB (Drug eluding bead)-TACE

cTACE: Administration of an anticancer agent emulsified in ethiodized oil, followed by embolization of the tumor-feeding artery with gelatin sponge particles.
TACE with drug-eluting beads (DEB-TACE): Administration of spherical drug-eluting microspheres loaded with an anticancer agent.

Compared with conventional TACE, drug-eluting bead TACE is a drug delivery embolization technique that permits fixed dosing with the ability to provide sustained release of anticancer agents over a period of time.
Better tolerated but survival benefit in question...
C-TACE better 1-month and 3-month survival

Ikeda M et al JVROSG-1302 PRESIDENT study Liver Cancer 2022;11:440–450
Radioembolization: Yttrium-90 microspheres

- Microspheres, 25-30 microns: preferentially trapped in the tumor capillary bed
- Staging angiogram performed 7-10 d prior to Y90
  - Identify variant anatomy and determine optimal catheter position
  - Determine pulmonary shunting
- Median time to response
  - 1.2 mo (necrosis)
  - 6.6 mo (decrease size)
- Areas of interest
  - Down-staging
  - Radiation lobectomy
  - PVT

Due to the fact that it is, microembolic, seen on this angiogram pre- and post-, the hepatic arteries maintain flow allowing for it to be safely administered in patients with portal vein thrombosis. Emerging good data peritransplant impacting outcomes

Potential Complications Y90

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prevention</th>
</tr>
</thead>
</table>
| Delivery of radiation to nontargets (eg, gastric ulcers, cholecystitis) | • Prophylactic coil embolization  
  • Proper catheter placement  
  • Avoid reflux of microspheres  
  • ? Proton pump inhibitors |
| Post-radioembolization syndrome           | No proven therapy                               |
| Hepatic dysfunction (radiation-induced liver disease) | • Patient selection  
  • Selective or super-selective infusion  
  • Avoid whole liver treatment |
| Biliary AE: necrosis, abscess, stricture  | Avoid if compromised sphincter of Oddi          |
| Radiation pneumonitis                    | Activity adjustment to decrease lung dose  
  • Contraindicated if >30 Gy with 1 treatment OR >50 Gy cumulative |

Systemic Treatments for HCC: From Dirt to Plenty

**TYROSIN KINASE INHIBITORS:**
- **Tumor growth suppression** mediated by targeting serine/threonine kinases that are components of the Raf/MEK/ERK pathway (e.g., C-Raf, wild-type B-Raf, and mutant V600E B-Raf), a common downstream pathway of signals transduced via VEGFR, PDGFR, and EGFR;
- **Angiogenesis suppression** by targeting tyrosine kinases (e.g., VEGFR1, VEGFR2, VEGFR3, PDGFR-α/β, RET, and Fms-related tyrosine kinase 3)
- First Line: *Sorafenib, Lenvatinib*
- Second Line: *Regorafenib, Cabozantinib*

**IMMUNE CHECKPOINT INHIBITORS:**
- ANTI-PD-1 antibodies: Nivolumab and Pembrolizumab,
- Anti-PD-L1 antibodies: Avelumab, *Durvalumab*, and *Atezolizumab*
- AntiCTLA-4 antibodies: Ipilimumab and *Tremelimumab*

**MONOCLONAL ANTIBODIES:**
- Anti VEGFR2: Ramucirumab
- Anti VEGF-A: *Bevacizumab*
Systemic Therapy: Current Paradigm

Well selected patients with Child-Turcotte-Pugh B cirrhosis may be offered sorafenib, lenvatinib, or single-agent anti-PD1 or anti-PD-L1 immune checkpoint inhibitor therapy. (Level 3, Weak Recommendation)

First/Second Line
- Atezolizumab + Bevacizumab
- Tremelimumab + Durvalumab
- Sorafenib or Lenvatinib

Second/Third Line
- Regorafenib/ Cabozantinib/ Ramucirumab (AFP>4000)
- Nivolumab + Ipilimumab

Contraindications for immunotherapy
- Autoimmune disorder
- Liver transplantation
- High risk of gastrointestinal/esophageal bleeding

Adapted from Llovet JM et al, Nature Cancer 2022
Curative Treatments

Resection
- Noncirrhotics
  - Choice of therapy
- Cirrhotics
  - Reserved for CTP A
  - Avoid R hepatectomy
- Best for solitary HCC
  - < 30% eligible
- Survival
  - 5 yrs: 70%
- Recurrence
  - 5 yrs: 70%

Ablation
- Effective when < 3 cm
- Multiple modalities
  - Thermal
  - Chemical
  - *Stereotactic radiation*
- Minimally invasive
- Survival
  - 5 yrs: 40% to 50%
- Recurrence
  - 5 yrs: 70%

Transplant
- Cures both
- MELD exception
  - Milan criteria
  - Downsizing
- Demand > supply
- Survival
  - 5 yrs: > 70%
- Recurrence
  - 5 yrs: 15%

Survival
- 5 yrs: 70%

Recurrence
- 5 yrs: 70%


Biologically Aggressive HCC

- Features
  - Microvascular invasion
  - Satellite nodules
  - Diffuse infiltrating growth
  - Poorly differentiated
  - Mixed cholangiocarcinoma
  - Bad molecular signature
  - FDG-PET scan positive
  - High AFP and AFP-L3%
  - Rapid growth

- Associated with
  - Early metastasis
  - High risk of recurrence after resection or liver transplantation
  - Failure of local control with RFA/TACE
  - Poor prognosis

There is no consensus on how to incorporate biology into tumor staging

Holistic Care of the Liver Cancer Patient

- Nearly 1 in 3 patients with HCC have cachexia post diagnosis, including many with early-stage tumors, compensated cirrhosis and good performance status
- Cachexia was an independent predictor of worse survival; multimodal interventions may improve outcomes
Frailty Measurement Tools

**Liver Frailty Index:**
Consists of 3 performance-based measures:
- Grip strength,
- Chair stands, and
- Balance testing

Improves the ability of MELDNa to predict mortality in cirrhotic patients awaiting liver transplantation.

The Liver Frailty Index calculator is available at: [http://www.liverfrailtyindex.ucsf.edu/](http://www.liverfrailtyindex.ucsf.edu/)


**Nutrition Pearls**

**Energy needs are high**

<table>
<thead>
<tr>
<th>Body mass index (kg/m²)</th>
<th>Estimated daily recommended energy intake (kcal/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>≥ 35 kcal</td>
</tr>
<tr>
<td>30-40</td>
<td>25-35 kcal</td>
</tr>
<tr>
<td>≥ 40</td>
<td>20-25 kcal</td>
</tr>
</tbody>
</table>

- Consult with a registered dietician to measure your resting energy expenditure
- Calculate your estimated resting energy expenditure using an on-line calculator (www.wellnesstoolbox.co)

**Eat enough: Strategies**

- "I get full fast"
- "Food tastes different"
- "Low salt diet makes food taste bland"

**Strategies**

- Eat often (every 3-4h)
- High density foods (e.g., nuts, chia)
- Food variety – buy one new food at the store every time
- Add flavor – garlic, lemon, chili flakes, turmeric
- Relax salt restriction

**At the right time: Late evening snack**

- Ability to release sugar as fuel
- Breakdown of muscle to meet the body’s needs
- Malnutrition, muscle loss, frailty

Metabolic profile of a patient with cirrhosis after an overnight fast = Metabolic profile of a healthy person after 3 days starvation

Nutrition Pearls

**Of the right stuff: Protein intake**

<table>
<thead>
<tr>
<th>Body weight (use ideal weight)</th>
<th>Recommended daily protein intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>140 pounds (~63 kg)</td>
<td>~75-95 grams</td>
</tr>
<tr>
<td>180 pounds (~80 kg)</td>
<td>~100-120 grams</td>
</tr>
<tr>
<td>220 pounds (~100 kg)</td>
<td>120-150 grams</td>
</tr>
<tr>
<td>250 pounds (~110 kg)</td>
<td>130-165 grams</td>
</tr>
</tbody>
</table>

Strive to maintain recommended daily protein targets even if on caloric-restriction for weight loss.

**GREAT SOURCES**

- Chicken (3 ounces): 30 g
- Greek yogurt (1 cup): 20 g
- Tofu (1 cup): 20 g
- Lentils, boiled (1 cup): 18 g
- Edamame (1 cup): 17 g
- Salmon (3 ounces): 17 g
- Beans (1 cup): 15 g
- Almonds/pistachios (1/2 cup): 15 g

**GOOD SOURCES**

- Peanut butter (2 T): 8 g
- Quinoa (1 cup): 8 g
- Milk (1 cup): 8 g
- Penne (1 cup): 8 g
- Fish: 6 g
- Brown rice (1 cup): 5 g
- Sunflower seeds (1/4 c): 5 g
- Potato (1 medium): 5 g
- Chia seeds (1 T): 5 g

**OTHER FOODS**

- Avocado / guac: 4 g
- Broccoli (1 stalk): 4 g
- Carrots (1 ear): 4 g
- Wheat bread (1 slice): 4 g
- White rice (1 cup): 4 g
- Ice cream (1 scoop): 3 g
- Frozen yogurt (1 cup): 3 g
- Orange (1 cup): 2 g
- Banana: <2 g


---

Multi-disciplinary, Multi-facility Liver Tumor Boards

Enhancing access, improving quality of care, aiding in complex decision making
Factors associated with reduced mortality:

- Subspecialist care by:
  - hepatologists (HR, 0.70; 95% CI, 0.63-0.78)
  - medical oncologists (HR, 0.82; 95% CI, 0.74-0.91), or
  - surgeons (HR, 0.79; 95% CI, 0.71-0.89)

- Review by a multidisciplinary tumor board (HR, 0.83; 95% CI, 0.77-0.90)

Our SCAN ECHO HCC Tumor Board Approach

Multidisciplinary multi facility discussion:

- Take into account CPT score/CSPH:
  - Below 7, CPT A with no CSPH we have many options
  - Above 7 no resection or SBRT, but MWA, TAE, TACE, TARE with transplant consideration

- Take into account tumor size:
  - Greater than 3 cm surgery or SBRT better options
  - Smaller than 3 cm multiple options with similar efficacy

- Take into account tumor location:
  - Dome tough to biopsy or ablate, surgery and SBRT better options
  - Central location, close to major vessels MWA less desirable

- Take into account patient comorbidities/age
- Take into account local expertise and availabilities
- Take into account transplant candidacy
- Take into account patient goals and wishes

HCC with aggressive biology:
- Poor differentiation,
- Rapid doubling,
- Vascular invasion
- Presence of satellites
  - High AFP
  - High neutrophil/lymphocyte ratio
  - Circulating tumor cells
  - Diffusion restriction on MRI
  - PET positivity

CPT Child Pugh Turcot
CSPH Clinically Significant Portal HTN
SBRT Stereotactic Body Radiation Therapy
THE CONTINUUM OF CARE
THE PATIENT IS AT THE CENTER

Identification of high risk groups
Liver disease diagnosis
Cirrhosis diagnosis
Suspicious lesion
HCC Diagnosis
HCC Treatment
Recurrence of HCC

PRIMARY PREVENTION
Eradication of HCV
Control of HBV
ETOH cessation/rehabilitation

SECONDARY PREVENTION
Control of Metabolic Syndrome
Improve Access
Evaluate barriers

SURVEILLANCE
Liver cancer
Multidisciplinary Regional Tumor Boards
Cancer navigation
Patient navigation
Support

PALLIATION
End of Life care

TAKE HOME POINTS

• Epidemiology is changing with eradication of hepatitis C and emergence of NAFLD/NASH with obesity epidemic.

• Screening needs to be refined with changing risk allocations and epidemiology.

• Imaging quality of contrast enhanced MRI and CT is crucial in diagnosis and management and standardized communication between radiologists and providers are crucial: LIRAD integration nationally.

• Resection, ablation via MWA, RFA, SBRT are curative options for small lesions in addition to surgical resection.

• Liver transplantation cures the cancer and underlying disease, limited by access. Refer timely.
TAKE HOME POINTS

• Multiple targeted therapies are available and in development.

• Combination regimens used timely and sequentially can improve overall survival. Do not delay transition to systemic therapy.

• Evaluation of nutritional status, sarcopenia, frailty with associated interventions are key to survival with good quality of life.

• Recognition of HCC with aggressive biology may avoid futile therapies.

• Palliative Care should be an integral part of management starting at time of diagnosis.

A multidisciplinary approach is the mainstay for complex decision-making

Questions?

Ayse Aytaman, MD, FACP

Janice Jou, MD
CONNECT AND COLLABORATE IN GI

ACG & CCF IBD Circle
ACG Hepatology Circle
ACG Functional GI Health and Nutrition Circle
ACG Women in GI Circle

ACG GI Circle
Connect and collaborate within GI

ACG’s Online Professional Networking Communities
LOGIN OR SIGN-UP NOW AT: acg-gi-circle.within3.com

81