

Updates in Hepatocellular Carcinoma

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Disclosures

The speaker has no disclosures.

Objectives

1. Understand the relationship between fatty liver disease, liver cirrhosis, and the development of liver cancer.
2. Identify clinical prevention and screening strategies for HCC.
3. Understand the importance of multidisciplinary evaluation, management, and treatment of HCC.

Can Liver Cancer Develop in a Patient without Cirrhosis?

YES

- Approximately 90% of primary liver cancers are HCC
- Typically arises in a background of chronic liver disease caused by:
 - HBV or HCV
 - SLD
- **MASH-HCC accounts for 20% of HCC in the Western world and is estimated to become the predominant etiology of HCC globally by 2030.**
- **By 2030, Hispanics are forecast to have the highest HCC rates among men and second highest among women.**

Huang, D. Q., El-Serag, H. B., & Loomba, R. (2020). Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nature Reviews Gastroenterology & Hepatology*, 18(4), 223–238. <https://doi.org/10.1038/s41575-020-00381-6>

Llovet JM, Willoughby CE, Singal AG, Greten TF, Heikenwalder M, El-Serag HB, et al.. Nonalcoholic steatohepatitis-related hepatocellular carcinoma: pathogenesis and treatment. *Nature Reviews Gastroenterology & Hepatology*. 2023;20(8):487–503.

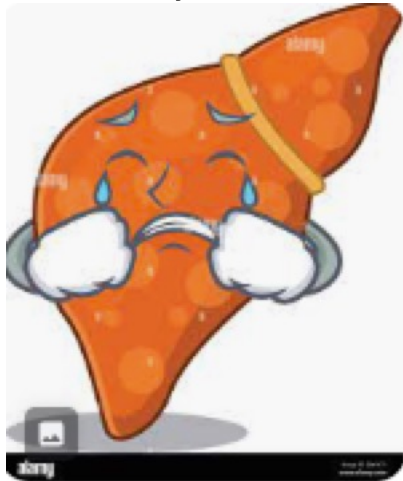
Clinical Management: Prevention

- Many observational, retrospective, population-based studies suggest:
 - Metformin: 22% HCC risk reduction
 - Statins
 - Coffee
 - Aspirin
- All play a role in HCC prevention regardless of liver disease etiology.
- All have an effect at the molecular level on tumorigenesis pathways.
- Coffee contains compounds that have an inhibitory effect on liver carcinogenesis



Clinical Management: Prevention

- Dietary Recommendations
 - Hypocaloric or Mediterranean diet COMBINED with moderate-intensity exercise to promote and sustain weight loss.
- Physical activity also correlates with a decreased risk of HCC.
- Currently NO direct evidence that weight loss reduces the risk of MASLD-associated HCC.



However, weight loss → steatosis reversal
and likely decreased fibrosis → reduced
HCC risk

Clinical Management: Prevention

Smoking: 20-86% increased risk of HCC for 30 years after smoking cessation

Diabetes alone, even without obesity, almost doubles the risk of HCC

- Very important to manage diabetes and hypertension

Treat HCV for cure

Treat chronic HBV if indicated

Clinical Management: Screening

- National and international guidelines
 - Cirrhosis or HBV: liver ultrasound and AFP (alpha-fetoprotein) tumor marker every 6 months
 - Patients with HCV cirrhosis who have been cured are at increased HCC risk for up to **10 years**
 - Surveillance is NOT recommended in:
 - Patients with a life expectancy of less than 1-2 years no eligible for liver transplant
 - Cured HCV patients WITHOUT cirrhosis
 - MASLD patients due to an annual incidence of HCC of 0.008 per 100 person-years
 - FIB-4 calculation is recommended in F1 and F2 fibrosis for screening

Diagnosis

IMPRESSION:

1. Arterially enhancing exophytic left hepatic lesion measuring 2.1 cm with delayed phase washout on pseudocapsular enhancement concerning for HCC (LR-5).
2. Cirrhotic liver without evidence of portal hypertension



Time 0: No Contrast



Arterial Phase



Portovenous Phase

Do we need to biopsy this mass?



Category	Description
LR-1	Definitely benign
LR-2	Probably benign
LR-3	Intermediate probability of HCC
LR-4	High probability of HCC, not 100%
LR-5	Definitely HCC
LR-5V	Definite venous invasion regardless of other imaging features
LR treated	LR-5 lesion status post-locoregional treatment
LR-M	Non-HCC malignancies that may occur in cirrhosis: metastases, lymphoma, cholangiocarcinoma, PTLD

Abbreviations: LI-RADS, Liver Imaging Reporting and Data System; HCC, hepatocellular carcinoma; PTLD, post-transplant lymphoproliferative disorder.

Key Phrases:

Arterial phase hyperenhancement

Portal venous washout

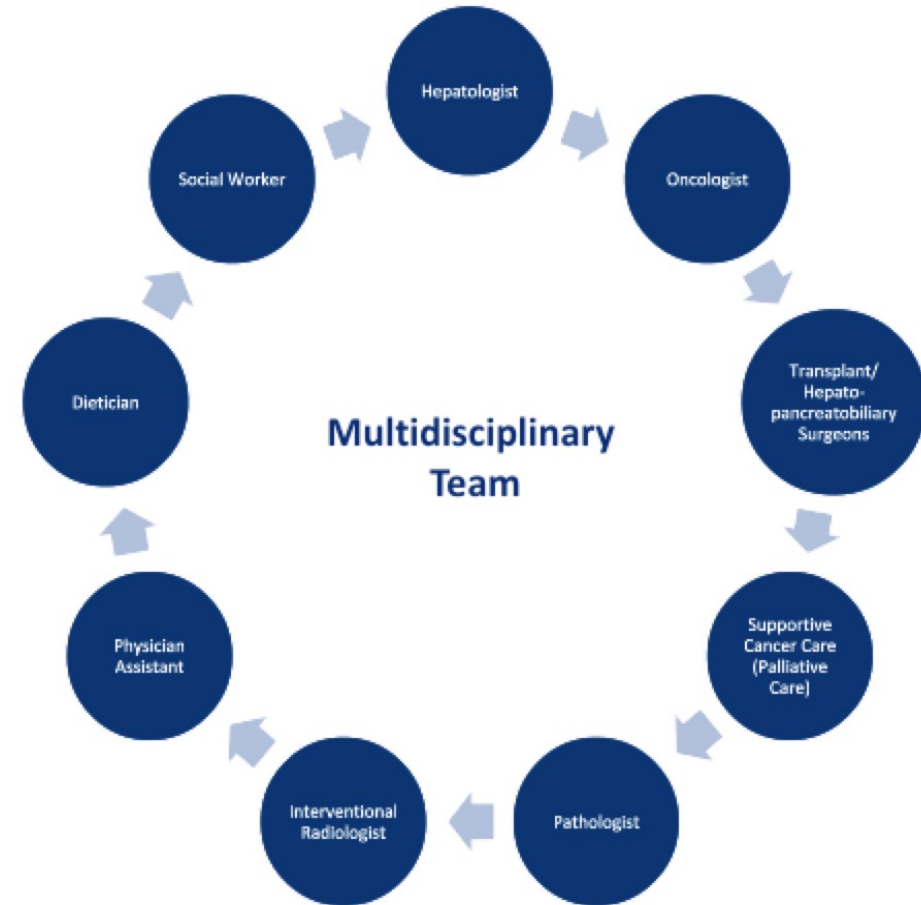
Pseudocapsule

LiRads 5

Your Patient has HCC: What's Next?

First recommendation from American Association for the Study of Liver Disease (AASLD) is to refer the patient to a center with Multidisciplinary Care.

“In conclusion, our study highlights that treatment delays are experienced by 10% to 20% of patients. Given an association between treatment delays and overall survival, interventions to reduce these disparities remain critical”.



Multi-D HCC Evaluation and Treatment

41.7% of management plans are changed after Multi-D evaluation.

“Some centers have transitioned to an interactive multidisciplinary team structure, such as a fluid referral system, in which patients are seen sequentially by specialists from different disciplines as needed, or co-located clinics, in which patients are seen concurrently by multiple specialties in a single visit.”



Treatment

Surgical Resection:

- Curative for patients with localized HCC **WITHOUT** cirrhosis as compared to those with cirrhosis
 - Lower post operative liver-related morbidity
 - Lower HCC recurrence rates
 - Higher disease-free survival
- 5 year survival may exceed 70% but larger tumor size is associated with increased risk of recurrence.
- *"Balancing oncologic outcomes and potential postoperative liver decompensation requires an experienced, multidisciplinary team assessment to optimize outcomes".¹*
- A one-year prospective cohort study in 2019 showed that pre-operative ctDNA showed promise for predicting recurrence after surgery and response to systemic therapies.²

1. https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx, pg 27

2. Fu Y, Yang Z, Hu Z, et al. Preoperative serum ctDNA predicts early hepatocellular carcinoma recurrence and response to systemic therapies. *Hepatol Int.* Aug 2022;16(4):868-878. doi:10.1007/s12072-022-10348-1

Liver Transplantation: DDLT or LDLT

THE CURE!

Who is eligible??

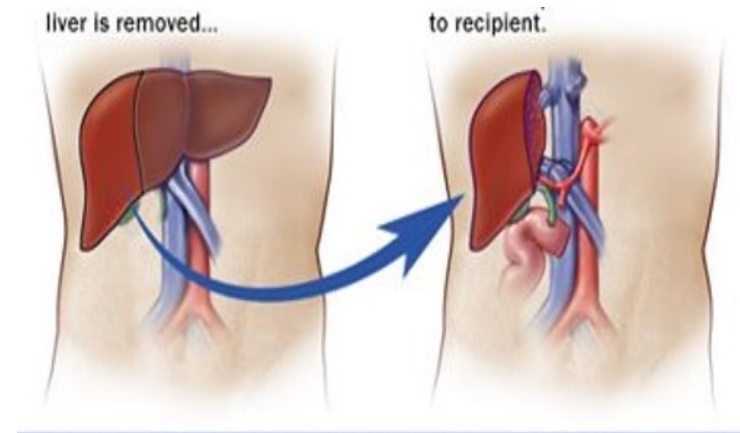
Early-stage HCC who are not resection candidates due to:

- Liver dysfunction
- Multiple tumors

Within MILAN Criteria:

- 1 tumor > 2 cm but \leq 5 cm in size
- 3 or more tumors > 1 cm but \leq 3 cm
- No vascular invasion
- No extrahepatic metastases

10-year median survival and 10% risk of recurrent cancer, significantly lower than resection



What About Those Out of Milan?

Downstage the lesions to within Milan Criteria using local therapy

Interventional Radiology

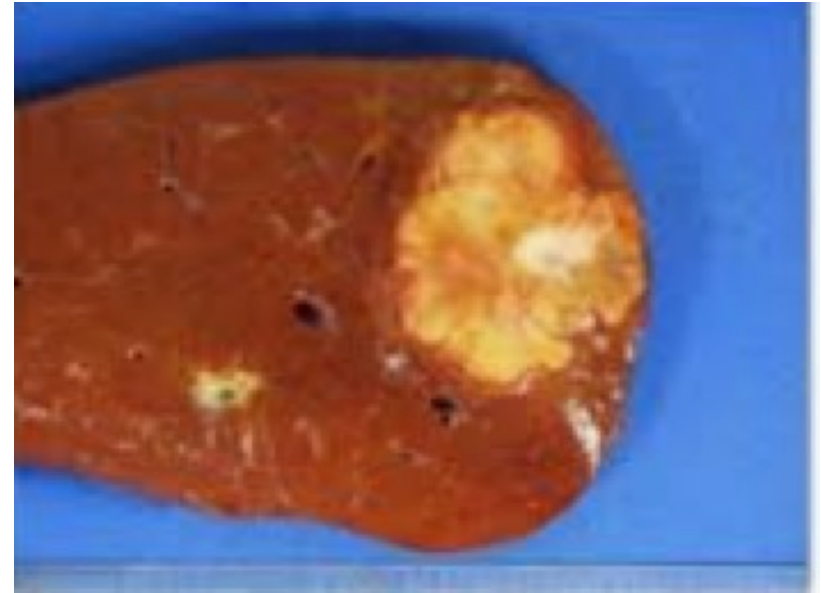
TACE: transarterial chemoembolization

TARE: transarterial radioembolization

Ablation: burning the tumor with microwaves or radiofrequency

Radiation Oncology

SBRT: Very targeted, external beam high dose radiation to the tumor



AFP > 1000 ng/ml must fall below 500 ng/ml

What if Transplant is Not an Option?

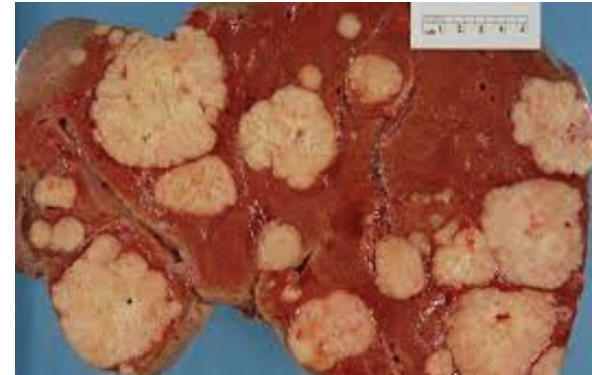
Local Therapy First

- TACE, TARE, Ablation, EBRT
- Modalities can be combined for optimal results
- 3 cm tumor or less, AASLD recommends thermal ablation
- If the HCC > 3cm then TACE, TARE, EBRT or ablation + TACE

Continue to treat locoregionally until disease progression or poor tolerance to treatment

Who Gets Systemic Treatment?

- Unresectable HCC who are not eligible for LRT due to:
 - Large tumor burden
 - Widely metastatic
 - Vascular invasion such as portal vein tumor thrombus
 - Disease progression despite LRT
- Must have a good performance status



GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

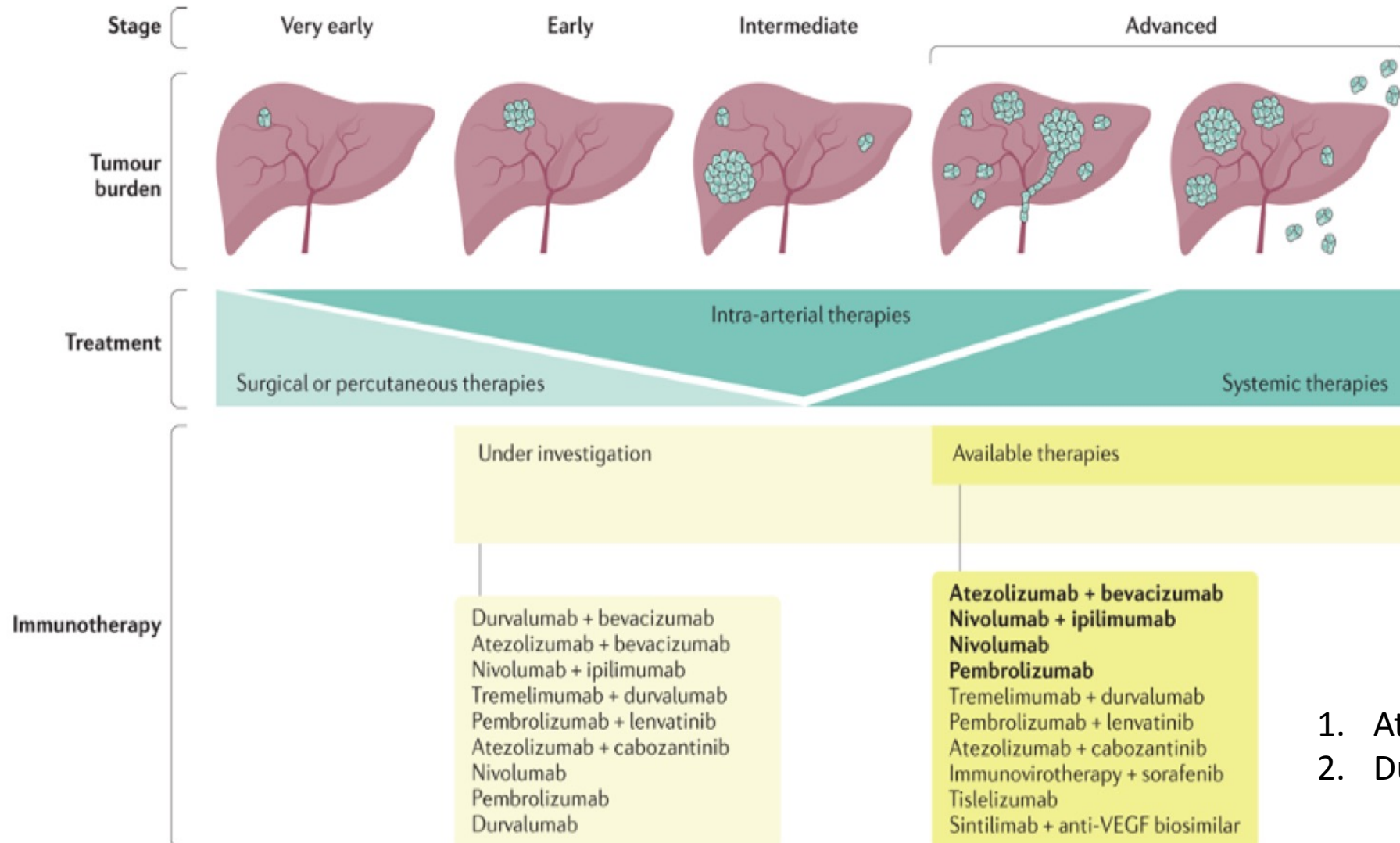
Who Gets Systemic Treatment?

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points) Class A = 5 to 6 points (least severe liver disease) Class B = 7 to 9 points (moderately severe liver disease) Class C = 10 to 15 points (most severe liver disease)			

Clinical Trials are on Child's Pugh A patients.

Many actual patients are Child's Pugh B

Shifting paradigms in treatment of HCC



Multi-modality is the key despite the stage!

1. Atezolizumab + Bevacizumab
2. Durvalumab + Tremelimumab

Summary

- Hepatocellular carcinoma can occur without cirrhosis.
- First-degree relatives of MASH cirrhosis patients should be counseled regarding increased risk and offered screening.
- Hispanics and South Texas Hispanics are predicted to have the highest rates of HCC.
- Prevention:
 - Mediterranean diet COMBINED with moderate-intensity exercise for weight loss
 - Treat underlying liver disease
 - Stop Smoking!!
 - Coffee, statins, metformin, aspirin

Summary

- Surveillance
 - Cirrhosis or HBV: liver ultrasound and AFP every 6 months
 - NOT recommended in:
 - Patients with a life expectancy of less than 1-2 years not eligible for liver transplant
 - Cured HCV patients and MASLD patients WITHOUT cirrhosis or with F1 or F2 fibrosis
- If US finds a tumor then consider a CT three or four phase and AFP or refer the patient to hepatology or multidisciplinary liver center.
- Do not order a biopsy until after the appropriate cross-sectional imaging has been evaluated. Remember the LiRads criteria.

Treatment Summary

- Resection
- Liver Transplantation: DDLT or LDLT
 - Milan Criteria
 - Downstaging
- Locoregional options
 - Ablation
 - TACE/TARE
 - EBRT/SBRT
- Systemic Therapies
 - Multiple first line immunotherapy and combination options
- Multidisciplinary care is critical because most HCC cases require a combination of treatments initially or over time.

References

- <https://www.aasld.org/new-nafld-nomenclature>
- Llovet JM, Willoughby CE, Singal AG, Greten TF, Heikenwälder M, El-Serag HB, et al.. Nonalcoholic steatohepatitis-related hepatocellular carcinoma: pathogenesis and treatment. *Nature Reviews Gastroenterology & Hepatology*. 2023;20(8):487–503.
- https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx
- State Cancer Profiles. (2016). Cancer.gov. <https://statecancerprofiles.cancer.gov>
- World Health Organization. (2022). Obesity. World Health Organization. https://www.who.int/health-topics/obesity#tab=tab_1
- Fu Y, Yang Z, Hu Z, et al. Preoperative serum ctDNA predicts early hepatocellular carcinoma recurrence and response to systemic therapies. *Hepatol Int*. Aug 2022;16(4):868-878. doi:10.1007/s12072-022-10348-1

References

- Kimura T, Fujiwara T, Kameoka T, Adachi Y, Kariya S. The Current Role of Stereotactic Body Radiation Therapy (SBRT) in Hepatocellular Carcinoma (HCC). *Cancers (Basel)*. 2022;14(18):4383. Published 2022 Sep 8. doi:10.3390/cancers14184383
- Admin. (2020, June 8). Child-Pugh score | Digestive Disease Dashboard. Digestive Disease Dashboard. <https://digestivedashboard.nl/2020/06/06/child-pugh-score/>
- Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol*. Mar 2022;76(3):681-693. doi:10.1016/j.jhep.2021.11.018

Q&A/Panel Discussion
