Notable Grand Rounds
of the
Michael & Marian Ilitch
Department of Surgery

Wayne State University
School of Medicine

Detroit, Michigan, USA

Eliza W. Beal, MD,

HEPATOCELLULAR CARCINOMA

February 22, 2023

About Notable Grand Rounds

These assembled papers are edited transcripts of didactic lectures given by mainly senior residents, but also some distinguished attending and guests, at the Grand Rounds of the Michael and Marian Ilitch Department of Surgery at the Wayne State University School of Medicine.

Every week, approximately 50 faculty attending surgeons and surgical residents meet to conduct postmortems on cases that did not go well. That “Mortality and Morbidity” conference is followed immediately by Grand Rounds.

This collection is not intended as a scholarly journal, but in a significant way it is a peer reviewed publication by virtue of the fact that every presentation is examined in great detail by those 50 or so surgeons.

It serves to honor the presenters for their effort, to potentially serve as first draft for an article for submission to a medical journal, to let residents and potential residents see the high standard achieved by their peers and expected of them, and by no means least, to contribute to better patient care.

David Edelman, MD
Program Director
The Detroit Medical Center

and

Professor of Surgery
Wayne State University School of Medicine

Hepatocellular Carcinoma

Eliza W. Beal, MD

Surgical Oncologist
Karmanos Cancer Institute

February 22, 2023

The talk from which this paper was derived was delivered by Dr. Beal at the Wayne State University School of Medicine Surgical Grand Rounds on February 22, 2023.

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer death worldwide.[1] The prognosis is dismal – with only a 15% 5-year overall survival rate.

The exception is in patients who are diagnosed early and are candidates for potentially curative therapies. High-risk patients who undergo surveillance are diagnosed with earlier stage HCC, and are therefore more likely to receive potentially curative therapies and have improved survival.

Therefore, screening for HCC is important.

HCC most commonly occurs in patients with chronic liver disease, including cirrhosis (see **Figure 1**) from any etiology and chronic hepatis B without cirrhosis. Non-alcoholic fatty liver disease is playing an increasingly common role in the development of HCC. **Table 1** (on p. 2) gives a breakdown of the etiology.

Patients known to be high risk should undergo surveillance. The American Gastroenterological Association (AGA), the National Comprehensive Cancer Network (NCCN), the American Association for the Study of Liver Disease (AASLD), the European Association

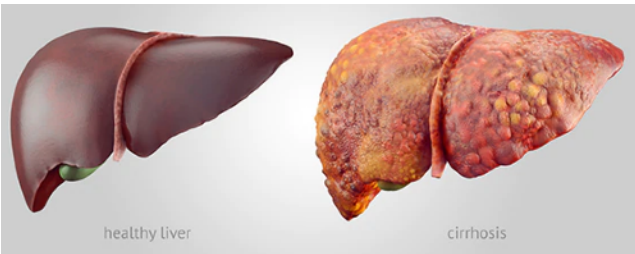


Fig 1. Healthy (L) vs. cirrhotic (R) liver
Source: National Institute of Diabetes and Digestive and Kidney Diseases. Cirrhosis. https://www.niddk.nih.gov/health-information/liver-disease/cirrhosis

1 Singal AG, Pillai A, Tiro J. Early Detection , Curative Treatment , and Survival Rates for Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis : A Meta-analysis. PLOS Med. 2014;11(4).
Yang B, Zhang B, Xu Y, Wang W, Shen Y, Zhang A, et al. Prospective study of early detection for primary liver cancer. J Cancer Res Clin Oncol. 1997;132:357–60.
Zhang B, Yang B, Tang Z. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417–22.

With Cirrhosis	Chronic Hepatitis B Without Cirrhosis
Chronic hepatitis B (including patients with viral suppression) Chronic hepatitis C (including patients post-SVR) Alcohol-related Genetic Hemochromatosis Primary Biliary Cirrhosis Non-Alcoholic Steatohepatitis Autoimmune Hepatitis Cirrhosis From Other Etiologies	Asian males ≥ 40 Asian females ≥ 50 Family History of HCC African Persons ≥ 20

* SVR = Sustained Virological Response, HCC = Hepatocellular Carcinoma

Table 1. Patients at High Risk for HCC
Source: Data adapted from Kanwal F, Singal AG. Surveillance for Hepatocellular Carcinoma : Current Best Practice. *Gastroenterology* [Internet]. 2019;157(1):54–64. Available from: https://doi.org/10.1053/j.gastro.2019.02.049

for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver (APASL) all have slightly different guidelines on how this should be done.[2] However, in summary, they all recommend ultrasound (US), with or without alpha fetoprotein, every 6 months.

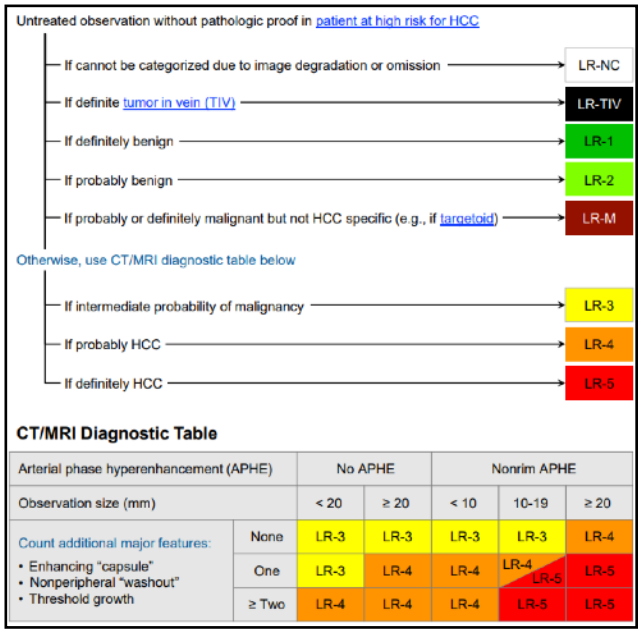
HCC Workup and Diagnosis

The following information on workup, diagnosis and management of HCC is in line with guidelines from the National Comprehensive Cancer Network.[3]

If there is a lesion < 1 cm on US without positive AFP, a repeat US should be obtained in 3 months. If there is a lesion > 1 cm on US and/or positive AFP, multiphasic abdominal CT or MRI should be obtained.

The classic imaging findings for HCC on CT and MRI are arterial enhancement, delayed washout and peripheral or capsular enhancement. HCC can be diagnosed on imaging. For patients with cirrhosis we use Liver Imaging Reporting and Data System (LI-RADS) criteria.[4]

The LI-RADS criteria use size and imaging features such as arterial phase hyperenhancement, presence of an enhancing capsule, nonperipheral washout and



CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

Fig. 2. LI-RADS-CT-MRI v2018.
Source: American College of Radiology. LI-RADS-CT-MRI v2018. https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/LI-RADS-CT-MRI-v2018

threshold growth to assign a category (see **Figure 2**). LI-RADS 4 is consistent with probable HCC and LI-RADS 5 with definite HCC. In practice, we treat LI-RADS 4 and 5 lesions as HCC.

If HCC is confirmed, additional workup should include a history and physical, a hepatitis panel, other labs including bilirubin, transaminases, alkaline phosphate, PT or INR, albumin, BUN, creatinine, alpha-fetoprotein.

Further staging should include CT A/P or MRI with contrast if this has not already been done, chest CT and consideration of a bone scan. Referral to a hepatologist should be considered based on laboratory findings, level of concern for cirrhosis and hepatitis status.

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2 Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD Guidelines for the Treatment of Hepatocellular Carcinoma. Hepatology. 2018;67(1):358–80.
Omata M, Norihiro AC, Masatoshi K, Jeong ML, Jia J, Tateishi R, et al. Asia – Pacific clinical practice guidelines on the management of hepatocellular carcinoma : a 2017 update. Hepatol Int. 2017;11(4):317–70.
EASL. EASL Clinical Practice Guidelines: Management of Hepatocellular Carcinoma. J Hepatol. 2018;69(1):182–236.
Covey AM. Hepatocellular Carcinoma : Updates to Screening and Diagnosis. J Natl Compr Cancer Netw. 2018;16(5):663–5.

3 NCCN Guidelines. Version 3.2022. Hepatobiliary Cancers. Hepatocellular Carcinoma. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

4 American College of Radiology. LI-RADS-CT-MRI v2018. https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/LI-RADS-CT-MRI-v2018

In order to stage the patient we consider liver function, performance status and tumor burden. Liver function can be quantified using Child–Pugh, MELD score or the Albi grade. Performance status can be quantified using the Eastern Cooperative Oncology Group (ECOG) or Karnosky performance status scales. Tumor burden can be described with the size and number of lesions.

Staging the patient in this way helps to determine the appropriate course of treatment.

Management of HCC

All patients who present with primary liver cancer should be evaluated by a multidisciplinary tumor board that includes gastroenterology or hepatology, surgical oncology, transplantation surgery, diagnostic and interventional radiology, medical oncology, and supportive/palliative care.

Potentially Resectable or Transplantable

For patients with HCC that is potentially resectable or transplantable, consider resection or locoregional therapy if the patient has appropriate performance status, is a Child–Pugh class A or B cirrhotic, does not have portal hypertension, the tumor is in a suitable location, the patient has adequate liver reserve and will have a suitable liver remnant after resection. **Figure 3** shows the types of resection.

For patients with Child–Pugh B cirrhosis that is more advanced, or Child–Pugh C cirrhosis, transplantation may be a better option. Standard criteria for transplantation for HCC include having an AFP < 1000, tumor 2-5 cm in diameter, or 2-3 tumors that are 1-3 cm in diameter, no macrovascular involvement, and no extrahepatic disease. There are extended criteria for transplantation used at some centers.

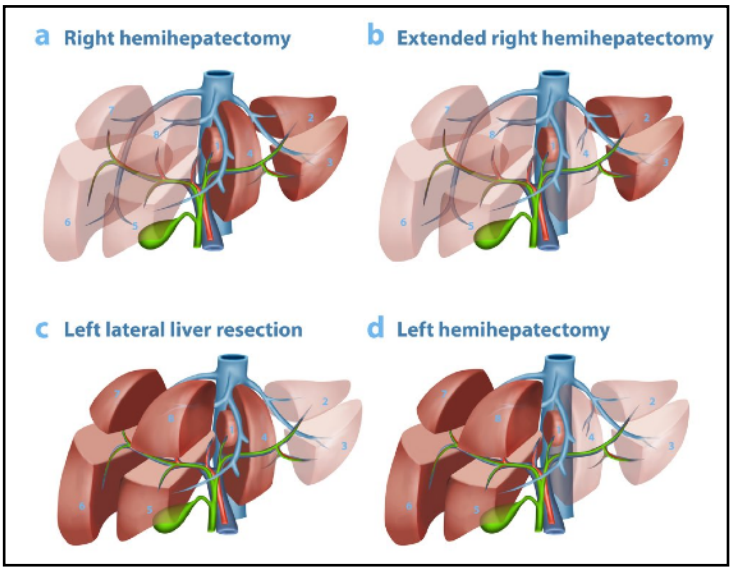

Fig 3. Types of Resection.
Source: Liver Surgery & Associated Treatments. Unattributed, undated web page at https://www.thesurgeonscollective.com.au/treatments/liver-surgery-liver-treatment-hepatitis-cancer-perth/

Locoregional Therapy

Locoregional treatment options for HCC include ablation, arterially directed therapies such as transarterial embolization (TAE), transarterial chemoembolization (TACE), TACE with drug eluting beads (DEB), yttrium-90 radioembolization, or external beam radiation therapy. The approach selected will depend on tumor size and distribution and proximity to major vessels or biliary structures.

Ablation can be performed percutaneously, laparoscopically, or open. The tumor must be in an accessible location. Ablation may be curative in tumors up to 3 cm. Lesions that are 3-5 cm can be treated in combination with other modalities. Lesions greater than 5 cm should be treated in combination with other modalities. Unresectable lesions > 5 cm should be treated with arterially directed therapies, systemic therapy or EBRT. There is no indication to use adjuvant sorafenib after ablation as it has not been shown to improve survival.

Arterially Directed Therapies

All tumors irrespective of location may be amenable to arterially directed therapies provided that the blood

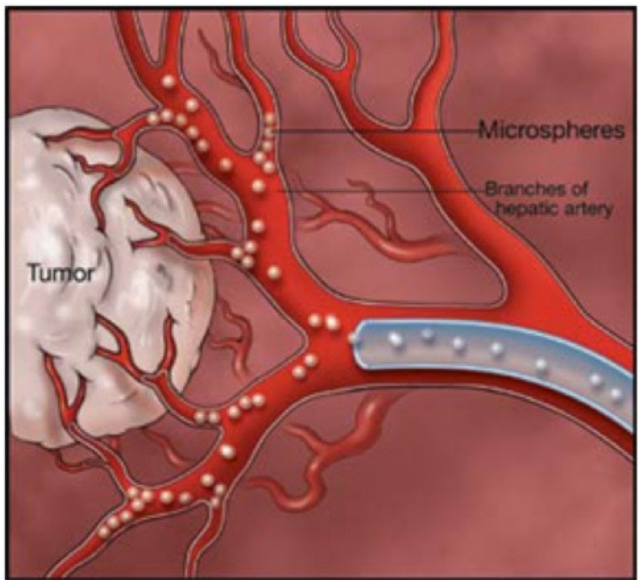

Fig. 4. Microspheres injected during trans arterial therapy "lock in" chemotherapy and block the blood supply too the tumor.
Source: Jain, Vikash. TACE. https://drvikashjain.com/tace

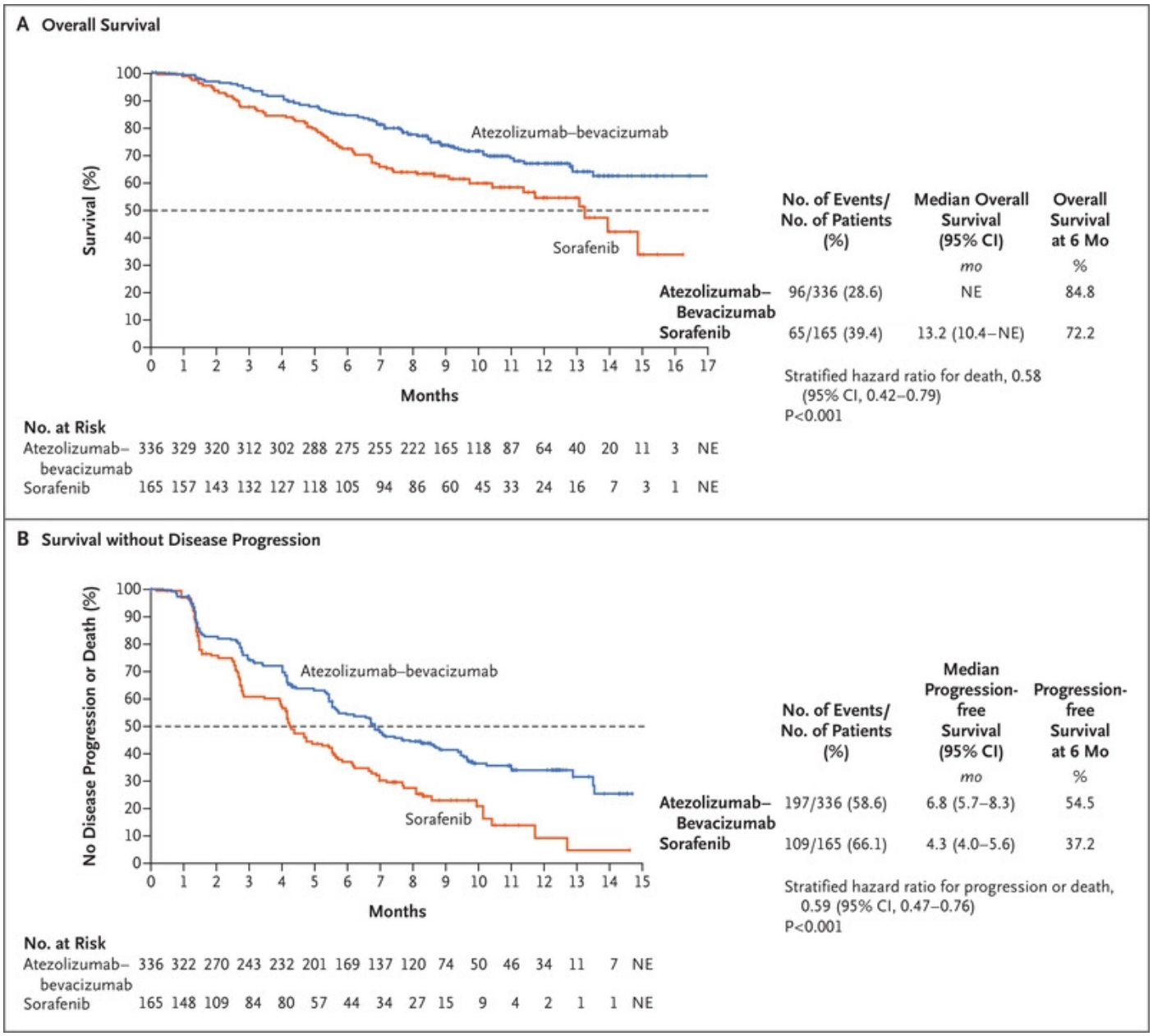

Fig. 5. Findings from the IMBrave 150 Trial.

Source: Table 3 in Finn, Richard S et al. "Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma." The New England journal of medicine vol. 382,20 (2020): 1894-1905. doi:10.1056/NEJMoa1915745

Variable	Atezolizumab–Bevacizumab (N=329)	Sorafenib (N=156)
	number (percent)	
Patients with an adverse event from any cause	323 (98.2)	154 (98.7)
Grade 3 or 4 event*	186 (56.5)	86 (55.1)
Grade 5 event†	15 (4.6)	9 (5.8)
Serious adverse event	125 (38.0)	48 (30.8)
Adverse event leading to withdrawal from any trial drug	51 (15.5)	16 (10.3)
Withdrawal from atezolizumab–bevacizumab	23 (7.0)	—
Adverse event leading to dose modification or interruption of any trial drug	163 (49.5)	95 (60.9)
Dose interruption of any trial treatment	163 (49.5)	64 (41.0)
Dose modification of sorafenib	—	58 (37.2)

Table 2. Adverse Events from Any Cause. *Source*: Table 3 in Finn, Richard S et al. "Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma." The New England journal of medicine vol. 382,20 (2020): 1894-1905. doi:10.1056/NEJMoa1915745

supply to the target tumor can be isolated without excessive non-target treatment. (See **Figure 4** on p. 3 for an example.)

Arterially directed therapies are relatively contraindicated in patients with total bilirubin > 3 mg/dL. Sorafenib may be appropriate following arterially directed therapy and has been shown in randomized controlled trials to provide benefit.

Surveillance after Resection
Patients who undergo resection, transplantation or locoregional therapy should be surveilled with imaging every 3-6 months for 2 years, then every 6 months. In conjunction, an alpha-fetoprotein (AFP) can be obtained. For patients with viral hepatitis, referral to a hepatologist should be considered.

Unresectable Patients
Patients may have unresectable HCC due to inadequate hepatic reserve, tumor location or extent of disease. These patients should be evaluated for transplantation. If they are not a candidate for transplantation, then locoregional therapy, clinical trials, systemic therapy or best supportive care are options. These options can also be considered for patients who are inoperable because of poor performance status, comorbidities, or with minimal or uncertain extrahepatic disease.

For patients with metastatic disease, clinical trials, systemic therapy or best supportive care should be considered.

IMBrave 150
The IMBrave 150 phase 3 trial studied patients with unresectable HCC who had not received prior treatment. Study patients were randomized to receive atezolizumab and bevacizumab or sorafenib.[5] (At the time, sorafenib was the standard of care.)

The primary endpoints in the trial were overall survival and progression free survival in the intention to treat population. Panel A in **Figure 5** (page 4) shows that patients who received atezolizumab and bevacizumab ("atezo-bev") had improved overall survival. Panel B shows that patients who received atezo-bev also had improved progression-free survival.

It is important to note that survival isn't everything: Patients who got atezo-bev also had decreased deterioration of quality of life. **Table 2** (page 5) shows that patients who got atezo-bev had a similar rate of grade 3, 4, and 5 adverse events in comparison to those getting sorafenib.

[5] Finn, Richard S et al. "Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma." *The New England journal of medicine* vol. 382,20 (2020): 1894-1905. doi:10.1056/NEJMoa1915745

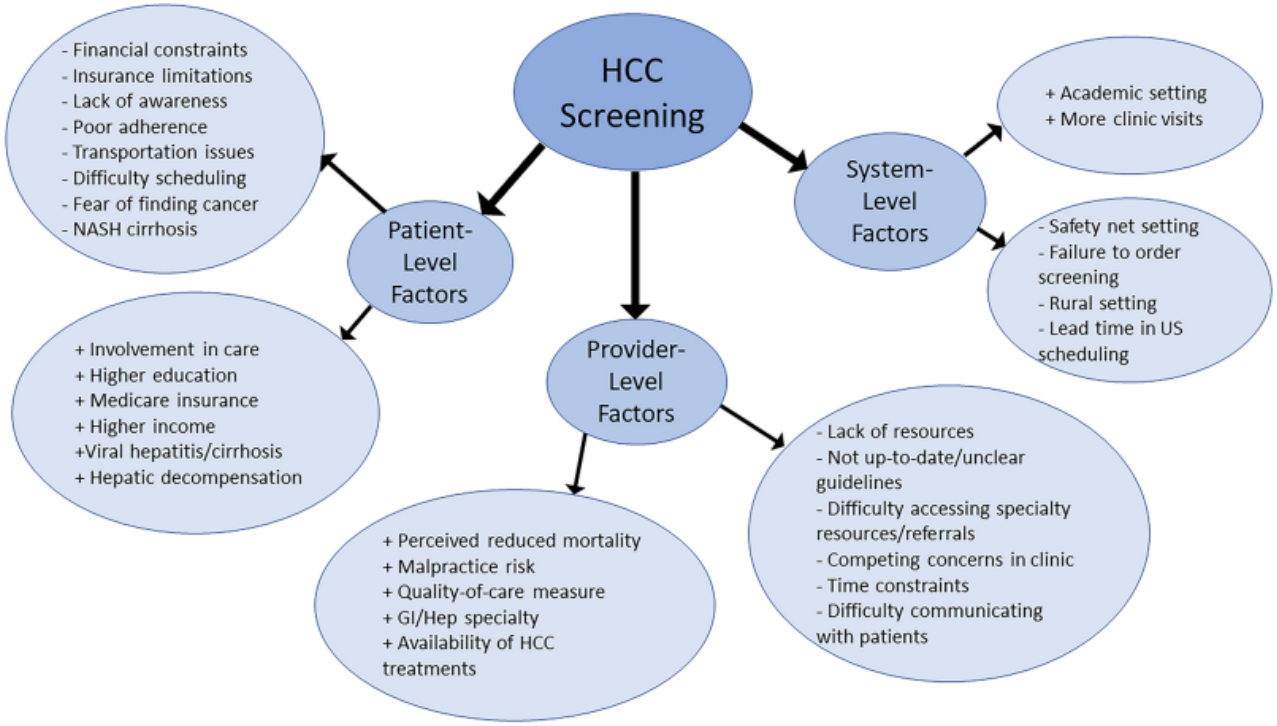

Fig. 6. Concept map illustrating factors positively and negatively associated with completion of HCC surveillance.

Source: Fig. 2 in Beal EW, Owen M, McNamara M, McAlearney AS, Tsung A. Patient-, Provider-, and System-Level Barriers to Surveillance for Hepatocellular Carcinoma in High-Risk Patients in the USA: a Scoping Review. J Gastrointest Cancer. 2022 Jul 26. doi: 10.1007/s12029-022-00851-x. Online ahead of print. PMID: 35879510

For patients who don't quality for atezo-bev, other options include sorafenib, lenvatinib, durvalumab, or pembrolizumab.

Options for subsequent line therapy for patients who progress on first line therapy are:
- Regorafenib (Child–Pugh A only)
- Cabozantinib (Child–Pugh A only)
- Remucirumab (Child–Pugh A only)
- Lenvatinib (Child–Pugh A or some B)
- Sorafenib (Child–Pugh A or some B)

Other:
- Nivolumab + Ipilimumab (CP A only)
- Pembrolizumab (CP A only)Use of these drugs is limited to patients with Child–Pugh A or B cirrhosis. There are not good systemic treatment options for patients with advanced cirrhosis.

Barriers to Surveillance for HCC

Why are patients with cirrhosis who present with advanced stages of HCC not diagnosed earlier? What proportion of high-risk patients are being surveilled? And why aren't all high-risk patients surveilled?

Only 20% of eligible patients in the United States undergo guideline-concordant surveillance even though high-risk patients who undergo surveillance are diagnosed with earlier stage HCC, are more likely to re-

ceive potentially curative treatment and have improved survival.[6]

Beal, *et al* (2022)'s scoping review[7] of the existing literature on barriers to surveillance for HCC included studies published in English between 1900 and 2021 that examined barriers to screening for HCC in patients with cirrhosis or chronic liver disease. The review included 15 survey studies, 25 quantitative studies, and 3 that included components of both.

Barriers to/Facilitators of HCC Surveillance

The concept map at **Figure 6** on page 6 illustrates factors positively and negatively associated with completion of HCC surveillance identified in the literature at the patient, provider and system level.

At the patient level, financial constraints, insurance limitations, lack of awareness, poor adherence, transportation issues, difficulty scheduling, fear of finding cancer and NASH cirrhosis (versus other etiologies of cirrhosis) were identified as being negatively associated with HCC surveillance. Patient involvement in care, higher education, Medicare insurance, higher income, viral hepatitis/cirrhosis, and hepatic decompensation were positively associated with surveillance.

At the provider level, provider perception that surveillance reduces mortality and the perception of not surveilling patients as being a malpractice risk were positively associated with surveillance. Additionally, if HCC surveillance was a measured quality of care metric, the provider in question was a gastroenterologist or hepatologist and provider awareness of the existence of available treatment options for HCC were also positively associated.

The provider's perception of a lack of resources, providers not being up to date on guidelines or their perception that the guidelines are unclear, difficulty accessing specialty care or referrals, competing concerns in clinic, time constraints and difficulty communicating with patients were negatively associated with surveillance.

At the system level, patient care occurring in an academic setting and patients having more clinic visits were positively associated with surveillance. Safety net settings, failure to order screening, rural settings and increased lead time in ultrasound scheduling were negatively associated.

Patient-, Provider- and System-Level Barriers to HCC Surveillance

A qualitative study[8] of 22 providers from internal medicine and family medicine, GI and hepatology used a semi-structured interview guide. Transcripts of the interviews were content-analyzed to reveal seven emergent themes, as follows:

1. Provider comfort with managing chronic liver disease and the relationships between hepatology, gastroenterology, infectious disease and primary care providers;
2. Provider knowledge of guidelines for HCC surveillance in high-risk patients and their knowledge about the impact that HCC surveillance can have
3. How providers discuss HCC surveillance with their high-risk patients;
4. Provider-Level barriers to surveillance;
5. System-level barriers to surveillance;
6. COVID-19; and
7. Patient-level barriers to surveillance.

Theme 1: The first theme was provider comfort with managing chronic liver disease and the relationships between hepatology, gastroenterology, infectious disease and primary care providers. In general, hepatology continues to follow patients with chronic hepatitis B, chronic hepatitis C and non-alcoholic steatohepatitis.

One hepatologist stated, "Mostly following them long term. Occasionally if I've answered the clinical question and their liver tests aren't bad, or you know, there's certain situations where I discharge them or for example, if you identify Hep C, they don't have advanced scarring and then you can discharge them after you cure the Hep C. But the majority I keep."

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[6] Beal EW, Owen M, McNamara M, McAlearney AS, Tsung A. Patient-, Provider-, and System-Level Barriers to Surveillance for Hepatocellular Carcinoma in High-Risk Patients in the USA: a Scoping Review. J Gastrointest Cancer. 2022 Jul 26. doi: 10.1007/s12029-022-00851-x. Online ahead of print. PMID: 35879510

[7] A scoping review is a systematic review that combines multiple different types of evidence – such as quantitative and qualitative data – and therefore does not usually include a meta-analysis.

[8] Beal EW, Gorji L, Volney J, Sova L, McAlearney AS, Tsung A. Provider- and System-Level Barriers to Surveillance for Hepatocellular Carcinoma Among Patients with Chronic Liver Disease. Poster Presentation. Society of Surgical Oncology 2022 – International Conference on Surgical Cancer Care. March 2022. Dallas, TX.
Beal EW, Gorji L, Volney J, Sova L, McAlearney AS, Tsung A. Patient-Level Barriers to Surveillance for Hepatocellular Carcinoma Among Patients with Chronic Liver Disease from the Provider Perspective. National Comprehensive Cancer Network 2022 – Annual Conference. March 2022. Virtual.

Non-hepatologists reported varying comfort levels taking care of patients with chronic liver disease from, “Not comfortable,” to “Fairly comfortable.”

One primary care provider stated, “I generally do the labs, and the right upper quadrant ultrasound, and if I see fatty liver, I do transplant elastography and if it comes back showing higher risk than I refer them on”

Primary care providers and gastroenterology report good relationships with hepatology and clear and easy communication.

One PCP stated, “Yeah, it's really easy to get people in and I get clear communication back. And so it's very clear what needs to happen next. And a lot of times in the future I'll order all the stuff ahead of time before the patient goes to their appointment, just to make things a lot easier for them”

Provider beliefs about which provider type is responsible for HCC surveillance varied. The majority of PCPS, gastroenterologists and infectious disease providers believed that the responsibility for HCC surveillance in high-risk patients is shared.

One primary care provider stated, “I think it needs to be shared thing. If the patient is only with primary care, the primary care provider has to keep, has to take ownership of the patient. But if hepatology is following along, then I expect them to also like make sure that the patient is following up on their screenings”

The majority of hepatologists and hepatology NPs believed that HCC surveillance is the primary responsibility of a patient’s hepatology team (5 of 7, 71%). One hepatologist stated, “I honestly do think it should be hepatologist because I think that, you know, someone has cirrhosis, they should follow them long term in a hepatology clinic...that sort of contact I think is very important because you're also not just looking at cirrhosis, you're looking at screening for varices, so many other things that again I think a yearly visit with someone in hepatology clinic or GI”

Theme 2: The second theme was provider knowledge of guidelines for HCC surveillance in high-risk patients and their knowledge about the impact that HCC surveillance can have. Providers reported varying levels of familiarity with guidelines for HCC surveillance. Four of four (100%) of hepatologists, 3/3 (100%) hepatology NPs, 2/3 (75%) gastroenterologists, 1/1 (100%) infectious disease providers, 3/7 (43%) of internal medicine physicians, and 1/1 family medicine NPs reported using the American Association for the Study of Liver Disease (AASLD) Guidelines. Two of seven (29%) internal medicine physicians reported using Up-to-Date. Hepatologists and hepatology NPs were also more likely to report being involved in updating the guidelines, reviewing the guidelines regularly and could more commonly summarize the guidelines.

One hepatologist stated, “"So, [for] all the patients with cirrhosis particularly, I follow the AASLD guidelines. So all the patients with cirrhosis, all the patients with Hepatitis B virus infection.”

Theme 3: The third theme that we identified is how providers discuss HCC surveillance with their high-risk patients. All provider types report discussing HCC surveillance with their high-risk patients in varying levels of detail.

One hepatologist reported, “Every time I talk to them, I try to make them realize about the importance of the surveillance. Always I tell them that the reason is to actually screen for HCC and diagnose it early, because early diagnosis is the key to successful treatment. We give them a booklet about cirrhosis and its’ different complications and screening tests and I do actually add in the AVS [After Visit Summary] about the information on their HCC screening."

And one internal medicine physician commented, “Well, I talk to them that you would be in an at-risk category, definitely having more knowledge is better than not enough so that we can make good choices in terms of your options. I mean, just because we find it doesn't necessarily mean we have to do something about it. But having that knowledge helps us give you better options to make better choices."

Theme 4: Several provider level barriers were identified including 1) knowledge, 2) time in clinic, 3) competing issues in clinic, and 4) deferral of responsibility

In regards to provider knowledge, one family medicine physician noted, “The other thing is, I'm just maybe this is going to come up, but like, I'm always like, well who gets an ultrasound? Who gets an MRI? Who gets a fibro scan? Who gets a? Yeah, that's where I get kind of confused. I'm like okay, I just follow whatever they said to do but I'm like, I'm not sure…Clearly, I’m identifying a knowledge gap in my own practice."

Providers also identified time in clinic as a provider level barrier to HCC surveillance, with one family medicine NP reporting, “Your schedule, patient load, and if you only have 20 minutes with patients coming in to see you for what is important to them. If you go into the room thinking, okay, I'm going to go over this, this, and this. The patient is there for something that they're concerned about that has nothing to do with

your list. You may end up having to follow up with them on that at another time."

Competing issues in clinic was also noted to be an important barrier with an infectious disease physician stating, "I think at least for primary care providers a lot of patients of a lot of things going on so I can see how it can be pushed under the radar as a less urgent issue. And then every six months is actually, you know, pretty frequent screening."

Deferral of responsibility, or not knowing what type of provider is taking responsibility can also be a barrier with one internal medicine doctor reporting, "I don't know if a lot of doctors, a lot of like primary care doctors see it within the scope of their practice. And so, they'll just like, refer, like offload, all of that to infectious disease or hepatology."

Theme 5: The three system level barriers that were identified were the absence of technology tools, insurance denial of surveillance imaging and difficulty scheduling surveillance studies.

The most commonly reported system-level barrier was the absence of technology tools. Overall providers report that there are no technology tools that they use to help with HCC surveillance. One provider stated, "I don't use any order sets and I don't have any pop-up best practice alerts."

In regards to **insurance**, one provider stated: "Sometimes insurance questioning surveillance. You know, we just peer-to-peer and fight for it as much as we can."

In regards to **scheduling surveillance tests**, one provider stated, "The barriers I think also with the scheduling for the ultrasound of course can be improved upon. I think if there's maybe a little quicker and getting the patient's called and scheduled it's something that after they leave the office visit we just talked about so it's fresh in their mind. But then if a week or so goes past they don't hear anything, then it can get lost and they don't call to schedule it or something like that."

Theme 6: The sixth theme was the impact of COVID-19 on surveillance. Providers reported that patients delayed surveillance due to concerns about nosocomial infections if they were to come to the hospital. Additionally, there were obstacles to scheduling patient follow-up with the modality shifts to the use of more telehealth and increased use of patient portals. In response to whether COVID-19 has been a barrier to surveillance, a provider responded, "I am sure. I hear from my patients actually stories that they are unable to get the blood testing because of COVID-19. They are scared to go to the laboratory. They give the same explanation when they are unable to get the ultrasound as well. People are actually scared going to the facilities."

Theme 7: Providers also reported several patient-level barriers to surveillance.

For example, one provider noted "A lot of times patients have difficulty with digital literacy, language barriers especially my patients, or they don't speak, they don't all speak English, and location or drive. So, if I get them to agree to go to do the screening, from their standpoint there is the problem of, oh gosh, this is so far from my house. This is so far from where I live,"

Providers agreed that health literacy is a relevant consideration regarding HCC surveillance.
In response to whether health literacy impacts patient care, one provider responded, "100%. Not only on this matter, in every matter. But certainly the screening is probably the most likely affected and impacted by the lack of literacy in our population. I mean, in general, the basic, the proficiency in health literacy is less than 15 percent in the U.S. American population in general. And if you were to break it down by minorities and underrepresented communities, the disparity will be shocking and disappointing, at the same time. So, I don't necessarily think that screening is, of HCC, is only one impacted. But certainly comes at the bottom of the list because it's not also like marketed as others."

Provider Suggestions for Improvement

Providers also made several suggestions for improvement of HCC surveillance. These suggestions included improved patient education, improved provider education, mass media campaigns, improved use of technology, patient navigators, increased hepatology and primary care collaboration, and recommendation for surveillance in radiology reports.

As an example, in regards to patient education, one internal medicine physician stated, "Educating the patients more. Taking more time on it because again, it's not something that I necessarily spend a whole lot of time talking about when there's other things going on too."

Providers also suggested improving provider education, "I think it's just education. I don't feel like providers would be resistant to doing something that has this proven benefit for the patient and for survival rates. I think then it's kind of more like spreading the word, getting the word out there of this is what's nationally recommended and you know, it's evidence-based best practice."

Providers also suggested mass media campaigns, "You have mass media campaign about lung cancer, breast cancer, colon cancer. There is a colon cancer month. There's nothing that dedicated for liver cancer. So, I think that's where we need a national campaign actually, if you want to make an impact in reducing incidents as well as mortality. I mean, half of the patients who have liver disease, half of the patients who have Hepatitis C don't even know about it."

Next Steps

A planned study by myself and colleagues aims first to examine the quantitative relationship between self-reported social determinants of health and cancer health literacy with HCC screening in high-risk patients.

- We hypothesize that patients with concerns related to their family and home, money and resources and social or emotional health and/or those with lower health literacy will have lower rates of HCC surveillance.

Our second aim is to identify patient-reported barriers and facilitators to screening for HCC in high-risk patients.

- We hypothesize that there are unidentified barriers and facilitators to accessing HCC surveillance for high-risk patients from the patient and caregiver perspective.

To elucidate these we are going to use a novel qualitative methodology referred to as listening sessions in which a group of patients eligible for screening will be educated about screening and then barriers and facilitators will be elucidated.

Data collected at these sessions will form the basis for a grant application to design patient-centered interventions to improve HCC surveillance rates.

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