Screening for Hepatocellular Carcinoma

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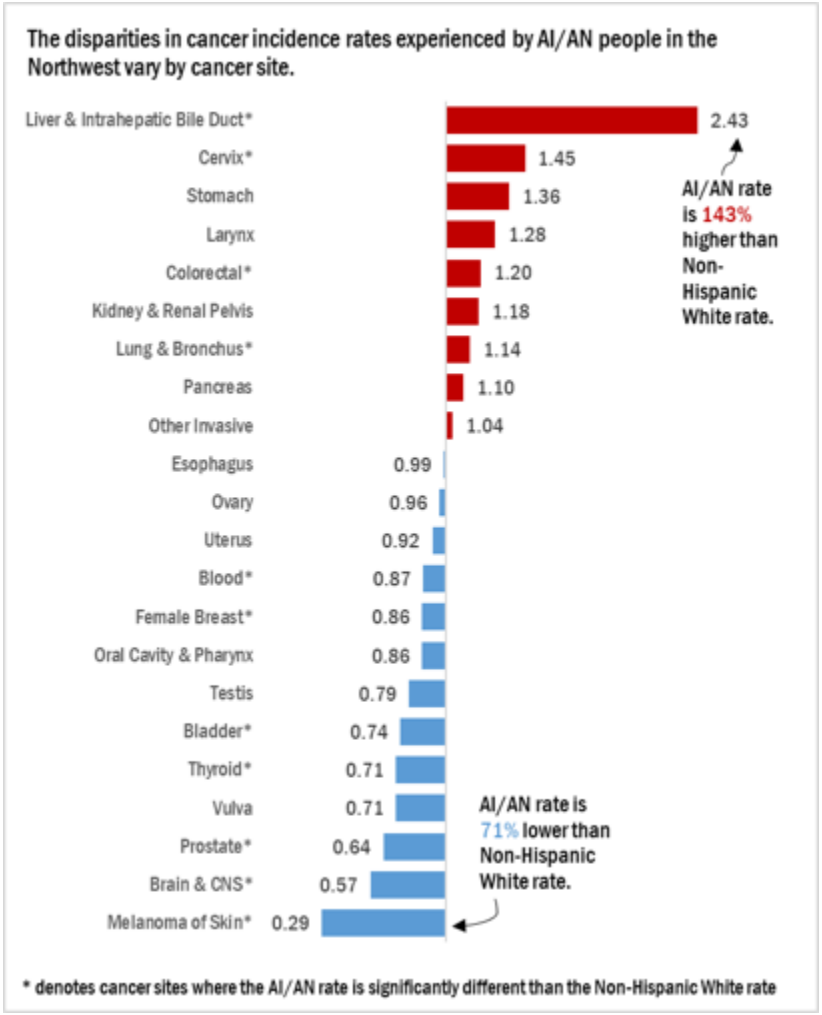
Hepatocellular carcinoma (HCC) is an important problem to address for AI/AN People



Cancer incidence for AI/AN People by sex, Northwest region, 2013-2017

Rank	Males	%	Females	%
1	PROSTATE	15.4%	BREAST	28.3%
2	LUNG & BRONCHUS	13.7%	LUNG & BRONCHUS	13.2%
3	BLOOD	10.9%	COLORECTAL	8.8%
4	COLORECTAL	10.8%	BLOOD	7.4%
5	LIVER & INTRAHEPATIC BILE DUCT	8.1%	UTERUS	6.9%
6	KIDNEY & RENAL PELVIS	6.1%	THYROID	4.6%
7	BLADDER	5.3%	KIDNEY & RENAL PELVIS	3.5%
8	ORAL CAVITY & PHARYNX	4.3%	PANCREAS	2.9%

Courtesy of Sujata Joshi

HCC screening likely improves survival

- Systematic review of 47 studies to include over 15,000 patients shows HCC screening increases early tumor detection and treatment with curative intent (surgery or ablation) and improved survival at 3 years (50.8% vs. 27.9%).[1]

- A VA Health System study did not demonstrate a survival benefit for patients with cirrhosis who had screening vs. not. Over 50% of tumors found in screening at early stage but only fewer than 15% had curative treatment.

Singal et al. *Plos Med.* 2014

Underutilization of HCC screening

- VA study including over 26,000 patients with cirrhosis showed they had up to date liver imaging only about 25% of the time during a median follow up of 4.7 years.[1]
- Mail outreach and patient navigation processes can improve screening rates, but rates are still low, only about 25% of patients have appropriate screening[2]

1. Goldberg et al. *Hepatology*. 2017
2. Singal et al. *Hepatology*. 2019

HCC screening – patients want it.

- No randomized control trials of HCC screening in patients with cirrhosis.
- In a pilot study of 205 patients for randomization 181 (88%) elected for non-randomization surveillance.

Poustchi et al. *Hepatology.* 2011

HCC screening – who gets it?

TABLE 1. PATIENTS AT THE HIGHEST RISK FOR HCC

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

Abbreviation: LYG, life-years gained.

Over age 40 →

Hep B carrier defined as HBsAg positivity

Hep B carrier with HDV co-infection should also undergo screening

Hep B carrier children can be screened if F3 fibrosis/cirrhosis or FDR FHx HCC

Marrero et al. *Hepatology*. 2018

HCC screening – unanticipated harms?

- 680 patients with cirrhosis with screening over a 3-yr period, ~10% had harms related to repeated CT/MR (9.7%) or biopsy (0.4%)[1]
- 999 patients followed for median 2.2 years, 69 (27%) had HCC, 187 (73%) had an indeterminant nodule, 32 (17%) experience harms by four or more cross sectional imaging studies or biopsy[2]

1. Atiq et al. *Hepatology.* 2017
2. Verma et al. Liver Transpl. 2018

Current guidelines

Table 1. Recommendations for cirrhotic adults

Continent	Guidelines	Modality	Time interval (months)	Exceptions
North America	AASLD-2017	US with or without AFP	6	Child-Pugh stage C unless awaiting liver transplantation
	CASL-2014	US	6	Same as AASLD
Asia	APASL-2017	US and AFP	6	Severe liver diseases/other co-morbidities (ineligible for curative therapy)
	CHINESE-2017	US and AFP	6	NS
	JSH-2015*	Extremely-high risk patients: (HBV/HCV cirrhosis)		
		- US and three Tm markers (AFP/PIVKA-II/ AFP-L3)	3-4	
		- CT or MRI (optional)	6-12	NS
		High risk patients: (cirrhosis of another etiology)		
		US and three tumor markers (AFP/PIVKA-II, AFP-L3)	6	
	JSH-LCSG-2014	Recommend EOB-MRI instead of CT or MR	Same as JSH	NS
Europe	EASL-2018**	US	6	Same as AASLD
	SPANISH-2016 (AEEH, SEOM, SERAM, SERVEI and SETH)	US	6	NS
	SEOM-2015	US	6	Same as AASLD
	ESMO-ESDO-2012	US	6	NS

*3rd JSH-HCC guidelines, 2013 update; **in press. HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: alpha-fetoprotein; NS: not specified; US: ultrasound; PIVKA-II: proteins induced by vitamin K absence; CT: computed tomography; MRI: magnetic resonance imaging; EOP-MRI: gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOBDTPA)-enhanced magnetic resonance imaging

Yilmaz et al. *Hepatoma Res*. 2018

HCC screening – imaging modality

- Currently ultrasound every 6 months
- 2 studies examined role of CT - no significant change in detection as compared to US
- 2 studies examined the role of MR – this is more sensitive and specific than US, but cost and time-consuming.
  - Perhaps an abbreviated MR protocol for HCC screening in on the horizon.

Kanwal and Singal. *Gastroentrol*. 2019

HCC screening – serological markers

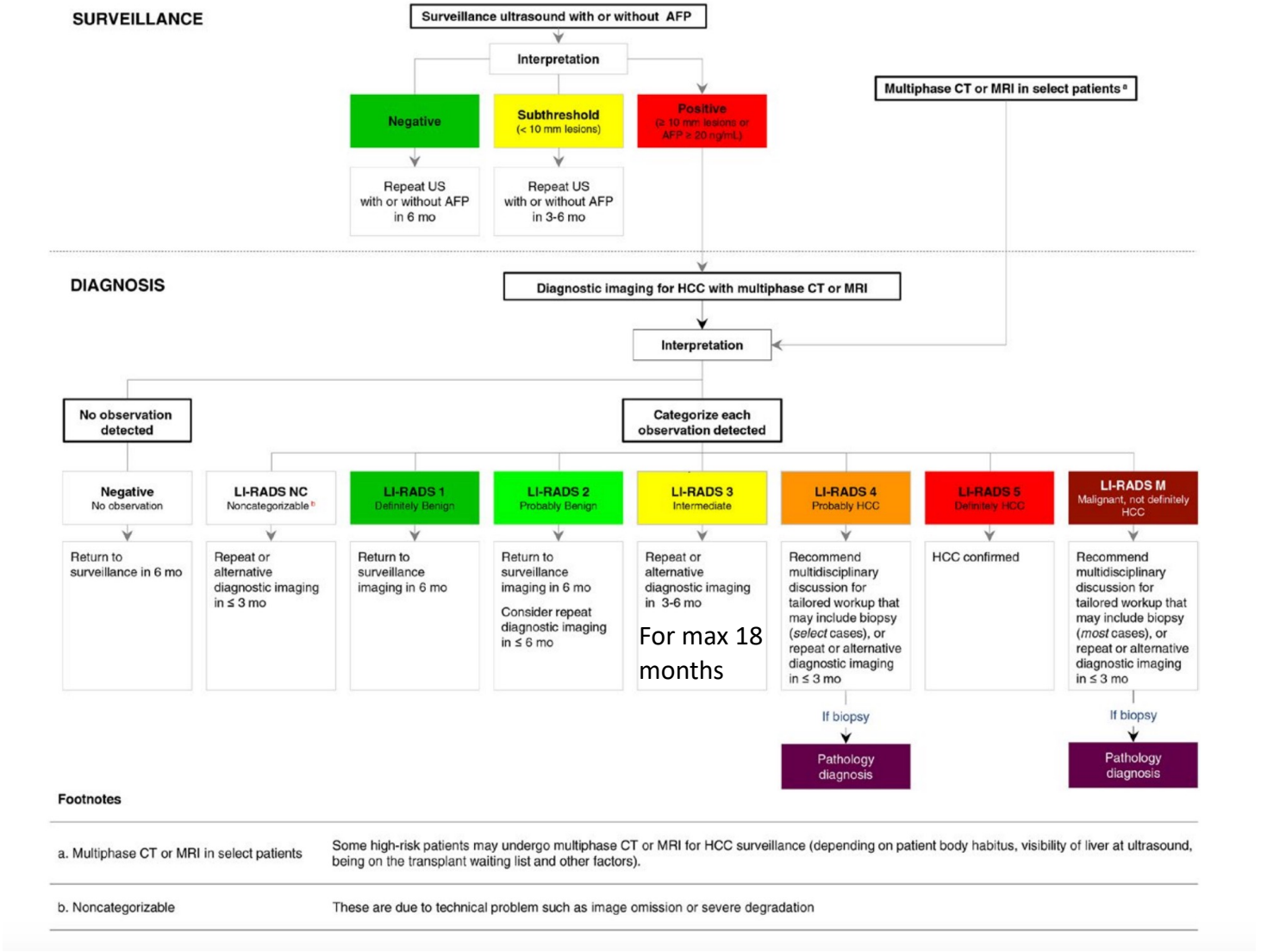
- Current guidelines don’t require alpha fetoprotein (AFP)
- Threshold cutoff of 20 ng/mL (our labs say it is abnormal above 5 ng/mL)
- Some have argued for adjusted AFP thresholds depending on the underlying cause of cirrhosis, ie 59 ng/mL with HCV vs. 11 ng/mL for non-HCV

HCC screening – screening interval, 3 month vs. 6 months vs. 1 year

- 510 patients screened at 6 months vs. 139 patients screened at 12 months showed a median survival difference of 40 vs. 30 months when corrected for lead time bias.[1]
- There is no difference in outcome with screening done at 3 months vs. 6 months.[2]

1. Santi et al. *J Hepatol*. 2010
2. Trinchet et al. *Hepatology*. 2011

Positive screening result lead to diagnostic imaging



Marrero et al. *Hepatology*. 2018

Preferred Management of LiRADS 4 lesions

- If LiRADS 4 on CT multiphase liver, then obtain MR multiphase liver, or vice versa. Attempt to get a diagnosis with LiRADS 5 without need for biopsy.
- Liver biopsy if neither modality shows a LiRADS 5 lesion
- Looking at expression of three proteins, glypican 3, heat shock protein 70, and glutamine synthetase, in biopsy specimen can help distinguish high-grade dysplastic nodules from well-differentiated HCC with about 80% sensitivity and 100% specificity.

Di Tommaso et al. Hepatology. 2007

Conclusions on screening for HCC

- US every 6 months with or without AFP
- Patients want it, but hard to get them to it
- Positive findings (lesion > 1 cm) on US or AFP greater than 20 ng/mL require diagnostic imaging with liver dedicated CT or MR and referral for multidisciplinary for LiRADS 4, 5 (even 3s are ok)

Thank you

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