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New Biomarkers For Improved HCC Surveillance

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Today's Topics

- Background on Hepatocellular Carcinoma (HCC)
- What is HCC surveillance?
- Can existing HCC surveillance programs work?
- How can we improve HCC surveillance?
- What can you do?

Epidemiology of Hepatocellular carcinoma (HCC)

Underlying cause for HCC is usually identifiable

		Predominant Risk Factor Areas			
Chronic liver diseases Type	%age cause of HCC	Asia	Africa	Western Countries	Japan
Chronic HBV infection	52%	◆	◆		
Chronic HCV infection	20%			◆	◆
Non-viral hepatitis leading to cirrhosis (alcoholic and non-alcoholic)	-	-	-	-	-

HCC facts

- 80% of all HCC cases arise from cirrhosis of the liver



- Annual HCC incidence rate in cirrhotic patients is 2-6%
- The overall HCC 5-year relative survival rate for 1996-2004 was 11.7%

Source: National Cancer Institute, SEER Cancer Statistics
<http://seer.cancer.gov/statfacts/html/livibd.html>. Accessed November 18, 2008.
Llovet JM, Bruix J. *J Hepatol*. 2008;48:S20-S37.

HCC incidence is rising

- HCC is the third most common cause of cancer related deaths worldwide
- Age-adjusted US incidence has increased >2-fold: 1985-1998
- National Cancer Institute statistics for liver cancer in 2009
 - Estimation of new cases: 22,620
 - Estimation of deaths: 18,160
 - The age-adjusted incidence rate was 6.6 per 100,000 (02-06 data)
 - 5th leading cause of cancer deaths in males

Source: National Cancer Institute, SEER Cancer Statistics
<http://seer.cancer.gov/statfacts/html/livibd.html>. Accessed January 15, 2010 ,
El-Serag HB, Hepatol Res 2007;37(suppl.2):S88-S94.

Current AASLD surveillance guidelines

Definition:

Surveillance is a serial screening of patients at risk for development of HCC (using the screening tests)

- Proposed in 2005
- Ultrasound (US) as a main tool
- AFP alone only if US not available
- 6-12 months interval

Surveillance useful only if curative therapies are available

HCC surveillance recommended for following groups of patients

Hep B carriers (+/- cirrhosis)

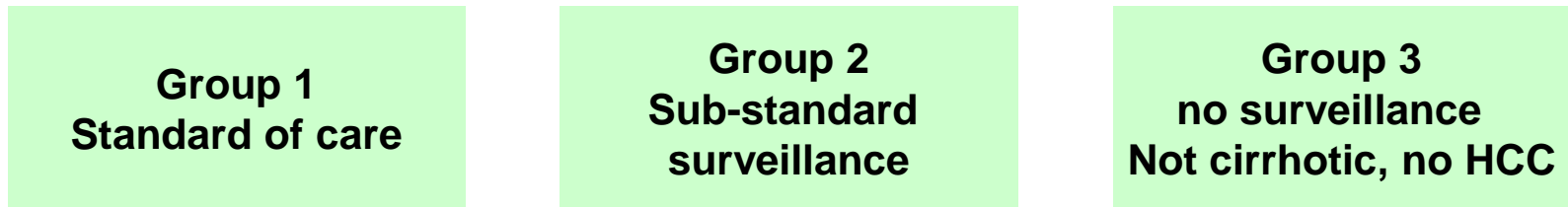
- Asian males \geq age 40
- Asian females \geq age 50
- All cirrhotic HBV carriers
- Family history of HCC
- Africans > age 20
- High HBV DNA

Non-Hep B cirrhosis

- Hepatitis C
- Alcoholic cirrhosis
- Primary biliary cirrhosis
- NAFLD
- Autoimmune hepatitis

HCC surveillance improves patient outcome

- Surveillance enables early detection of HCC (Stravitz et al. 2008)
 - 269 patients with cirrhosis and HCC divided into 3 groups according to quality of surveillance (a retrospective analysis):



- Group 1 had the best three year survival rate after HCC dx

Early detection → Liver transplant → Improved outcome

- Reduction in HCC-related mortality (Zhang et al. 2004)
 - Biannual surveillance reduced HCC mortality by 37%

Source: 1) Stravitz RT et al. Am J Med 2008;121(2):119-126
2) Zhang B-H et al. J Cancer Res Clin Oncol 2004;130:417-422

Current HCC surveillance tools

	Sensitivity	Specificity	Notes	Reference
<p>Primary tool = Ultrasound</p> <ul style="list-style-type: none"> –Insufficient sensitivity for HCC surveillance –User dependent –Difficult to interpret in LC and Obese patients 	60%	97%	pooled 14 out of 2,524 studies using stringent criteria	Colli et al. 2006
<p>Ultrasound back up tool: Total AFP</p> <ul style="list-style-type: none"> –Poor clinical performance in early detection of HCC 	39 - 64%	76 - 91%	EASL 2000 HCC Guidelines	Bruix et al. 2001

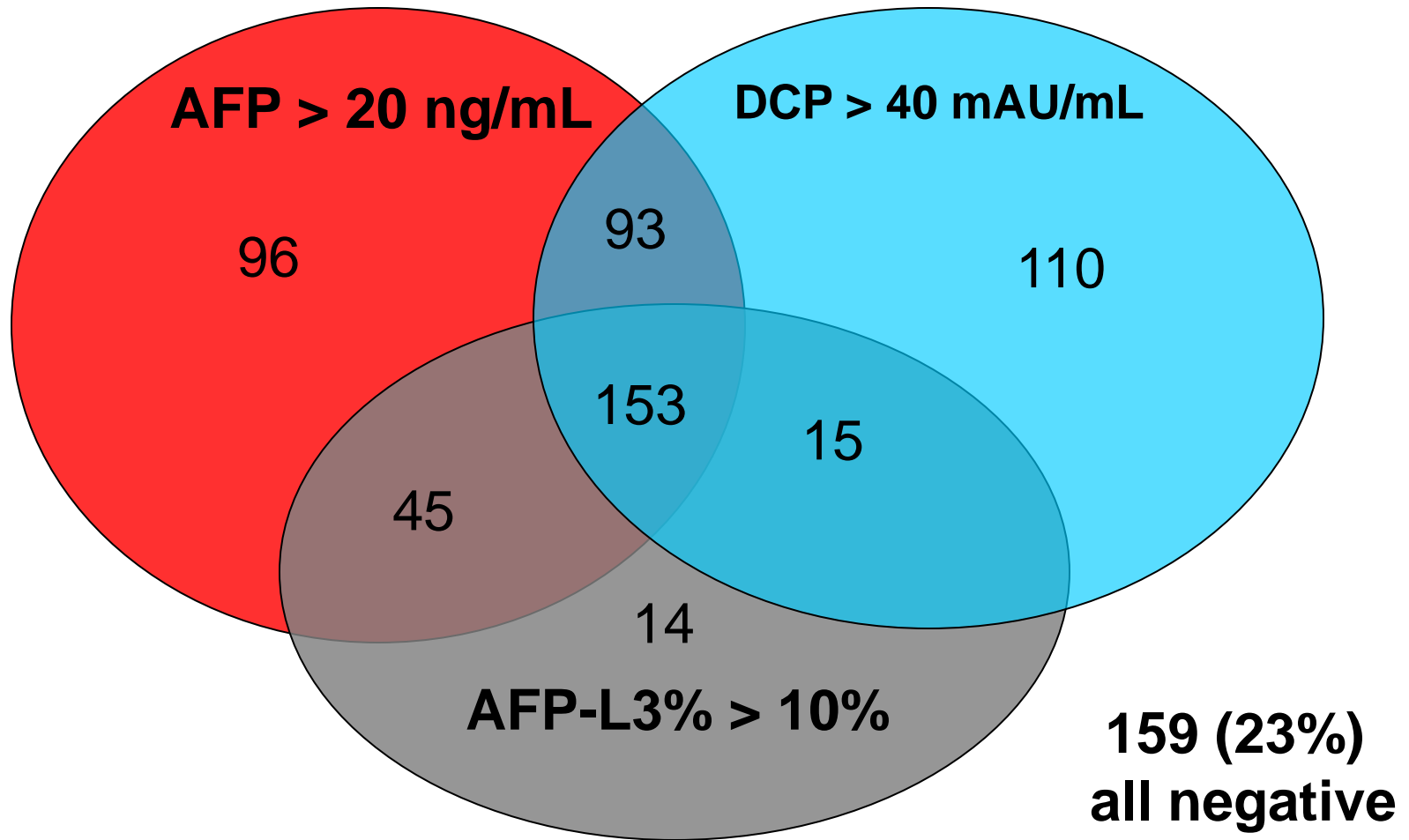
Source: 1) Colli A. et al. Am J Gastroenterol 2006;101:513-523
 2) Bruix J et al. J Hepatol 2001, 35(3):421-430



New HCC Surveillance Tools

- New tools are available for HCC detection
 - Minimally invasive serologic markers AFP-L3 and DCP (aka PIVKA II)
 - AFP-L3 and DCP are specific to HCC
 - Clinical data from the USA are mounting
 - FDA 510 (k) cleared
 - AMA accepted-Unique CPT codes
 - Commercially available through major reference labs in USA

Why use AFP-L3 and DCP in surveillance?



Source: Toyoda et al. Clin Gastro and Hep 2006;4:111-117

AFP-L3 has high specificity for HCC

	n	Sensitivity	Specificity	Note	Reference
Early recognition of HCC in patients with chronic viral hepatitis –AFP-L3% elevated 205 days before HCC diagnosis (20/39 patients) –AFP-L3 positive tumors had shorter doubling time (<90 days)	494	51%	92%	8.2 fold increase in relative risk for HCC dev in next 21 months	Sherman et al. 2005
Approaching 100% specificity at 35% cutoff for patients with 20- 200 ng/mL AFP	272	71%	63%	10% AFPL3 cutoff	Leerapun et al. 2007
Rule-out test using high NPV when imaging is inconclusive –Useful in 20-200 ng/mL total AFP range for HCV patients	372		87%	NPV:81%	Sterling et al. 2007

Source: 1) Sherman M, et al. Poster presented at: Digestive Disease Week, May 14-19, 2005; Chicago, Ill.

2) Leerapun, A., et al., Clin Gastroenterol and Hepatol 2007; 5:394-402

3) Sterling RK et al. Am J Gastroenterol 2007;102:1–10)

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DCP is highly accurate

	n	Sensitivity	Specificity	Reference
DCP differentiates cirrhosis from HCC	207	89%	96%	Marrero et al. 2003
Accurately identifies early stage HCC –DCP least affected by risk factors –DCP identified 13/15 patients who were AFP negative	253/ 52	86%/92%	93%/93%	Volk et al. 2007
Most accurate HCC marker available for HCC surveillance	240	86%	85%	Durazo et al. 2008

Source: 1) Marrero J. et al. Hepatology 2003;37:490
 2) Volk M. et al. Cancer Biomarkers 2007;3:79-87
 3) Durazo FA. et al. J Gastroenterol Hepatol. 2008;23(10):1541-1548

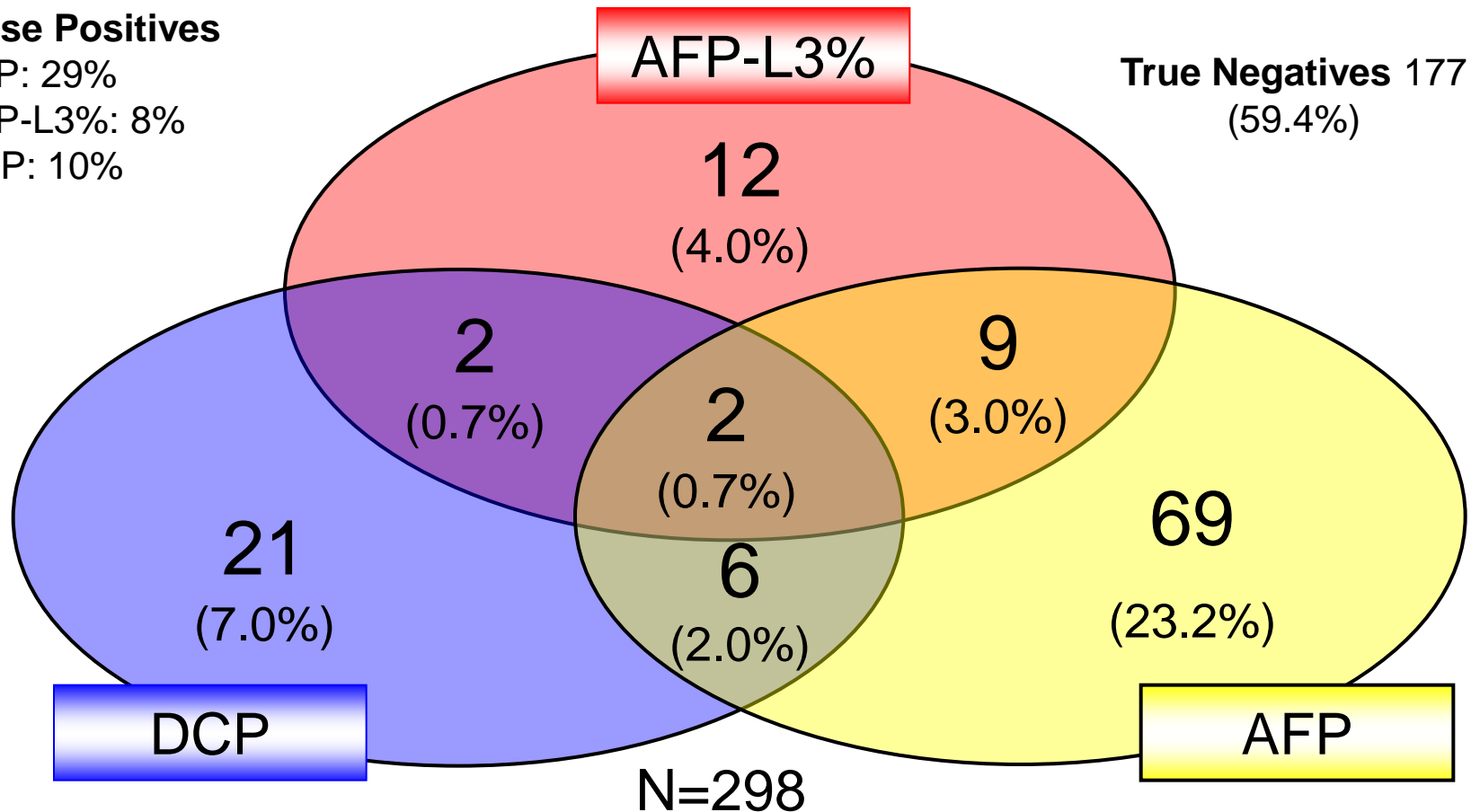
Combination testing decreases false positives

False Positives

AFP: 29%

AFP-L3%: 8%

DCP: 10%



HCC Risk panel

- “HCC Risk Panel” simultaneous measurement of AFP, AFP-L3 & DCP
- AFP-L3, AFP and DCP are complementary (Toyoda et al. 2006)
- Combination increases sensitivity (Carr et al. 2007)
- Each marker correlates to different tumor characteristics (Toyoda et al. 2006)
- Useful as additional tool in surveillance program & HCC management (Durazo et al. 2007)

Source: 1) Toyoda, H. et al. Clin Gastroenterol and Hepatol 2006; 4:111-117, 2) Carr B, et al. Dig Dis Sci. 2007; 52:776-782, 3) Durazo FA. et al. J Gastroenterol Hepatol. 2008;23(10):1541-1548

Conclusion

- HCC surveillance improves patient outcome
 - Enroll at-risk patients into surveillance program
 - Early detection of HCC and application of curative therapies
- AFP-L3 and DCP are effective additional HCC surveillance tools
 - Only partially overlapping, complementary
 - Identify additional patients who may not be detected using AFP only
 - Reduce false positives and needless enhanced follow up
- AFP-L3 and DCP are available **NOW**
 - FDA 510 (k) cleared
 - Unique CPT codes-CMS reimbursed
 - Available at major reference labs in the USA