

# Improved HCC Surveillance

## INTRODUCTION

Hepatocellular carcinoma (HCC) incidence in the United States is increasing. A study published in 2009 by National Cancer Institute (NCI) showed that age-adjusted HCC incidence rates tripled between 1975 and 2005 [1]. Moreover, despite the moderate improvements made over the past decades the relative five-year survival rate during 1999-2006 remained only 13.8% [2]. The poor five-year survival rate for newly diagnosed HCC is largely due to late diagnosis of liver cancer for which treatment options are limited.

## EARLY DETECTION IMPROVES PATIENT OUTCOME

Early detection of liver cancer is crucial for the application of curative therapies and improving patient outcome. Since the underlying cause of HCC is usually identifiable, patients who are at-risk for development of liver cancer are highly encouraged to enroll in HCC surveillance programs for early detection of HCC. A 2008 HCC surveillance study conducted in the USA concluded that the application of even a modest surveillance program for patients with cirrhosis can identify patients with early-stage HCC and suitable candidates for liver transplantation. In turn, HCC surveillance improves long-term, tumor-free survival of HCC patients receiving early treatment [3].

## HCC MANAGEMENT

HCC management guidelines from the American Association for the Study of Liver Diseases (AASLD) updated in 2010 recommend that patients be screened at 6 month intervals using ultrasonography [4]. Despite the high specificity of ultrasonography, the low clinical sensitivity limits ultrasonography as a surveillance tool. A 2006 systematic review of 14 ultrasonography studies (chosen from over 2,000 studies) estimated sensitivity and specificity at 60% and 97%, respectively. This meta-study concluded that "ultrasonography is highly specific but insufficiently sensitive to detect HCC in many cirrhotics or to support an effective

surveillance program" [5]. Even though new surveillance tools are available, official recommendations lag advances in newly available biomarkers. The addition of highly specific liver cancer biomarkers, lectin-affinity alpha-fetoprotein (AFP-L3) and Des-gamma-carboxyprothrombin (DCP), offer additional opportunities for early detection of HCC.

## HCC BIOMARKERS TO IMPROVE EARLY DETECTION OF HCC

DCP is an abnormal form of the coagulation protein produced by the liver. HCC cells lack the ability to convert this precursor to active coagulation protein thrombin. DCP is highly specific for HCC and complements AFP-L3% test in HCC detection [8-10]. For example, clinicians at the University of Michigan reported DCP's sensitivity and specificity of 92% and 93%, respectively, in differentiating early stage HCC from cirrhosis without HCC (Table 1). DCP also identified 15 of 17 patients (88%) with early stage HCC that would have been missed with total AFP measurement at 20 ng/mL cutoff [10].

AFP-L3, a glycosylated variant of AFP which has an additional  $\alpha$ 1-6 fucose residue, has proven to be a highly specific HCC biomarker. AFP-L3% test measures the percentage of AFP as the L3 glycoform. A North American population based prospective study demonstrated AFP-L3% having a specificity of 87% and negative predictive value (NPV) of 81% in patients with elevated total AFP (20-199 ng/mL) [6]. The study demonstrated that the HCC incidence was higher in patients with elevated AFP-L3 than in those with elevated AFP. In addition, AFP-L3%'s high NPV allows HCC-rule out when AFP and ultrasonography results are indeterminate. Using a higher AFP-L3% cutoff of 35%, clinicians at Mayo Clinic were able to achieve 100% specificity, with no false positives [7].

Tandem measurement of DCP and AFP-L3% has been shown to increase the sensitivity for HCC detection while maintaining high specificity (>90%) [8-10]. Figure 1 illustrates the complementary nature of these HCC biomarkers [9]. Table 1 lists clinical performance when HCC biomarkers are measured in tandem [10]. Since not all HCCs make all three biomarkers, tandem measurement of all three HCC biomarkers will identify more HCC patients than with ultrasonography and AFP. Furthermore, simultaneous measurement of AFP-L3% and DCP is both practical and convenient. It is practical because expression of two biomarkers complement each other. It is convenient because serum concentrations of three HCC biomarkers (total AFP, AFP-L3%, DCP) can be measured with a single serum sample on a single analyzer.

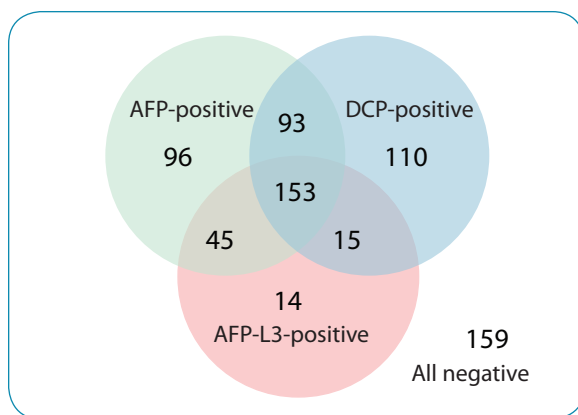


Figure 1: Distribution of HCC patients with various patterns of positivity for the 3 tumor markers of HCC [9]

All HCC (n = 84 HCC, 169 Cirrhosis)		
	Sensitivity	Specificity
AFP *	69%	91%
AFP-L3 **	57%	88%
DCP ***	86%	93%
All 3 markers	88%	91%

Early stage HCC (n = 52 HCC, 169 Cirrhosis)		
	Sensitivity	Specificity
AFP *	64%	92%
AFP-L3 **	50%	89%
DCP ***	92%	93%
All 3 markers	88%	91%

\*cutoff 23 ng/mL, \*\*cutoff 3%, \*\*\*cutoff 150 mAU/mL

Table 1: Clinical performance of HCC biomarkers when measured alone and when measured in tandem [10]

## COUNTER INDICATIONS [11]

For patients taking warfarin to lower the risk of blood clots, DCP will be markedly increased, since this drug works by blocking the action of vitamin K and leads to production of the same abnormal form of prothrombin as occurs in liver malignancies. If a patient has vitamin K deficiency, elevated DCP may also be seen.

A person with a persistent vitamin K deficiency or jaundice due to a liver obstruction may have elevated DCP levels that are not due to HCC. The anticoagulant warfarin and some broad-spectrum antibiotics can affect test results.

## REFERENCES

- 1 Hepatocellular Carcinoma Incidence, Mortality, and Survival Trends in the United States From 1975 to 2005. Altekruse et al., J Clin Oncol 27:1485-1491.
- 2 <http://seer.cancer.gov/statfacts/html/livibd.html>. Accessed December 8, 2010.
- 3 Surveillance for Hepatocellular Carcinoma in Patients with Cirrhosis Improves Outcome. Stravitz, et al., Am J Med. 2008 Feb;121(2):119-126.
- 4 Management of Hepatocellular Carcinoma: An Update. Sherman M, Bruix J., Hepatology 2010 July
- 5 Accuracy of Ultrasonography, Spiral CT, Magnetic Resonance, and Alpha-Fetoprotein in Diagnosing Hepatocellular Carcinoma: A Systematic Review. Colli et al., Am J Gastroenterol 2006;101(3):513-23
- 6 Clinical Utility of AFP-L3% Measurement in North American Patients with HCV-Related Cirrhosis. Sterling et al., Am J Gastroenterol 2007 Oct;102(10):2196-2205.
- 7 The Utility of AFP-L3% in the Diagnosis of Hepatocellular Carcinoma: Evaluation in a U.S. Referral Population. Leerapun et al., Clin Gastroenterol Hepatol. 2007 March; 5(3): 394–267.
- 8 Clinical Evaluation of Lens Culinaris Agglutinin-Reactive  $\alpha$ -Fetoprotein and Des- $\gamma$ -Carboxy Prothrombin in Histologically Proven Hepatocellular Carcinoma in the United States. Carr et al. Digestive Diseases and Sciences 2007;52:776-782.
- 9 Prognostic Significance of Simultaneous Measurement of Three Tumor Markers in Patients with Hepatocellular Carcinoma. Toyoda et al. Clinical Gastroenterology and Hepatology 2006;4:111-117.
- 10 Risk Factors for Hepatocellular Carcinoma May Impair the Performance of Biomarkers: A Comparison of AFP, DCP, and AFP-L3 Volk et al., Cancer Biomarkers 2007;3:79-87.
- 11 [www.labtestsonline.org](http://www.labtestsonline.org), accessed December 1, 2010.