



## Liver Cancer Surveillance Tools Can Enable Early Diagnosis

AFP Tests and Ultrasound Recommended for At-Risk Populations

By Maurizio Bonacini, M.D. and Laura Miyashita

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With the incidence of liver cancer (hepatocellular carcinoma or HCC) doubling over the past 20 years in the United States, there is an increased pursuit to identify new markers that can detect the disease in its early stages. This research, coupled with screening programs for at-risk populations, has the potential to reduce cases of chronic liver disease—which can ultimately contribute to the development of HCC.

#### At-Risk Populations

Recent studies have shown that patients at high risk for HCC and therefore, candidates for periodic surveillance include:

- chronic carriers of HBs Ag
- patients with cirrhosis
- patients with metabolic liver diseases
- individuals with family histories of HCC

While no randomized controlled trials have confirmed that surveillance reduces disease-specific mortality, screening the above populations is considered cost-effective and helpful in identifying patients with small tumors who could enroll in research trials.

#### HCC Surveillance Tools

The typical liver tests—ALT, AST, alkaline phosphatase and GGT—are not useful tools for monitoring HCC as large hepatic masses have few symptoms or biochemical abnormalities. Instead, ultrasound imaging and periodic monitoring of HCC markers such as alpha-fetoprotein (AFP) enable early identification of tumor development. “The long phase of asymptomatic tumor growth and the tumor’s tendency to grow as a solitary mass in many patients often enables early diagnosis of HCC,” explains Maurizio Bonacini, M.D., a hepatologist with California Pacific Medical Center’s Liver Disease Management & Transplant Program. He adds, “Even though typical liver tests have little impact on HCC diagnosis, any rapid change in bilirubin and/or alkaline phosphatase levels should lead to a speedy evaluation for HCC.”

An elevation in AFP—an a1-globulin that decreases after birth and reaches adult levels at one year of age (>10 ng/ML typically) signifies hepatocellular carcinoma, but can also signify hepatoblastoma, cholangiocarcinoma or massive hepatic necrosis.



In cases of fibrolamellar hepatocellular carcinoma, AFP levels are notoriously normal. To increase the sensitivity of AFP to 85%, the des-gamma-carboxyprothrombin (DCP) tumor marker is used in some institutions, particularly in Japan.

Periodic ultrasound examination offers the best HCC surveillance tool because it has more sensitivity and specificity than AFP. However, recommendations from recent conferences advocate:

- Older patients with cirrhosis or with certain congenital metabolic conditions known to be at risk for HCC should be screened by AFP determination and ultrasound twice a year.
- HBsAg carriers older than 35 years or with family histories of HCC should be screened for HCC by determinations of serum AFP levels and aminotransferase levels once a year (see table on page 3).

In patients with a rising AFP or liver enzymes, a more accelerated surveillance program may be implemented.

#### New Approaches

Presently, there is a tremendous interest and urgency to identify novel HCC diagnostic marker(s) that will

# Imaging Techniques Help Diagnose Previously Undetected Hepatic Tumors

Triple Phase CT Scan and Lipiodol CT Imaging Offer Advancements in Tumor Diagnosis

By William Harvey, M.D., radiologist and Laura Miyashita

As the treatment of liver lesions continues to evolve with more effective therapeutic options, it becomes increasingly important to accurately diagnose and characterize the extent of disease. Early diagnosis with subsequent transplantation before the development of large or infiltrative tumors offers the most effective treatment for hepatocellular carcinoma (HCC) because it can cure both the cancer and any underlying cirrhosis.

## Imaging Work-up

Imaging plays a major role in diagnosis because it helps differentiate HCC from other nodular lesions that may coexist, such as dysplastic or regenerating nodules. An initial imaging workup should include an ultrasound performed by a skilled ultrasonographer and triple phase (or “triphasic”) CT scan performed with a helical or a multidetector scanner that has rapid bolus intravenous contrast infusion capability (preferably at least at 3-5 cc/second).

“While the CT scan remains the best modality for HCC diagnosis, both ultrasound and magnetic resonance imaging (MRI) complement it, offering better evaluation of the hepatic vessels and detection of early portal vein invasion,” says William Harvey, M.D., radiologist at California Pacific Medical Center. He adds, “Ultrasound nicely demonstrates the morphologic changes of cirrhosis which are usually present with HCC. The tumor itself is usually heterogeneous and may contain areas of hemorrhage, necrosis or, much less frequently, calcification.”

California Pacific and most institutions use CT as the main imaging modality to evaluate the

liver for HCC. The initial imaging workup usually begins with a “triple phase CT” that involves:

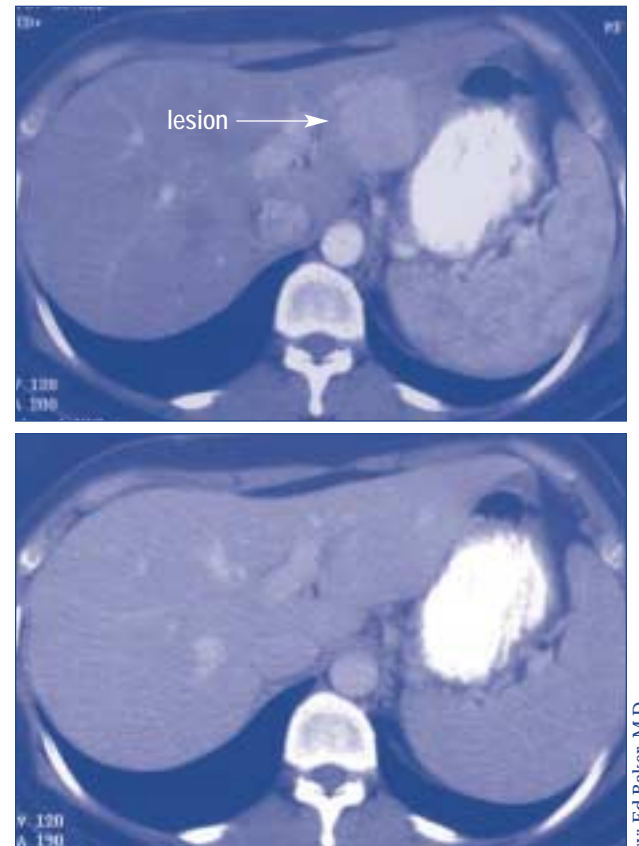
1. A non-contrast enhanced liver scan to show hemochromatosis, glycogen storage disease, amiodarone treatment or confluent fibrosis.
2. Hepatic arterial imaging (first 20-30 seconds of contrast injection) to view primary tumors that receive their blood supply from the hepatic arterial system.
3. Portal venous imaging (approximately 60-70 seconds after contrast injection) to confirm tumors with a rich arterial supply which will quickly fade during this phase and to help characterize other liver abnormalities.

To complement the CT scan, radiologists may use the T1 and T2 MRI weighting of different lesions. This helps differentiate between regenerative or dysplastic nodules and frank HCC, which is extremely important in deciding if a patient is an adequate candidate for transplantation.

The 3D volumetric imaging capabilities of the MRI allow radiologists to image in the axial, sagittal and coronal planes, offering increased anatomic evaluation of the lesions, the liver and its vascular supply, as well as the biliary system. This is often extremely beneficial to transplant surgeons.

## Lipiodol CT Scans

If, after initial imaging, confusion remains as to whether a lesion represents HCC or another hypervascular lesion (focal nodule hyperplasia, metastatic disease from carcinoid, islet cell tumors, etc.), a lipiodol CT scan can be used.



Two liver images from a triple phase CT. The first image (arterial phase) demonstrates a large hypervascular lesion in the left lobe of the liver. The second image (portal venous phase) demonstrates that the lesion is isodense to the liver and now much less apparent.

Courtesy: Ed Baker, M.D.

This technique involves an initial angiographic study of the liver’s arterial supply, followed by a small injection of lipiodol (a thick, oily substance that is an iodized ethyl ester of the fatty acid of poppy seed oil) into the hepatic artery. HCC nodules hold the lipiodol much longer than other cells, enabling radiologist to view these nodules during a follow-up CT scan performed seven to 28 days after the lipiodol injection. This technique has an accuracy rate of 88.3% and its sensitivity and specificity have been reported as high as 97.1 and 76.9%, respectively. ∞

## New Physicians Join Liver Disease & Transplant Team

By Laura Miyashita

California Pacific’s Liver Disease Management & Transplant Program continues to expand, with the following physicians joining our team:



John Rabkin, M.D.

### John Rabkin, M.D.

joins California Pacific as a liver transplant and hepatobiliary surgeon. He also serves in the departments of surgery at Legacy Good Samaritan Hospital and Providence

Medical Center in Portland, Oregon.

Dr. Rabkin is also a reviewer for the Annals of Surgery journal, a UNOS liaison to the American Society of Transplant Surgeons and Vice Chairman of UNOS’ Organ Procurement Organizations Committee. Dr. Rabkin received his medical degree at Boston University School of Medicine and postgraduate training at University of California, San Francisco. He is active in immunosuppression research for liver transplant patients and islet transplant research.

**Edward Doo, M.D.**, a hepatologist, comes to the Liver Program from the National Institutes of Health’s Liver Diseases Section, where his clinical work focused on treating chronic



Edward Doo, M.D.

hepatitis B and C infections, and laboratory work focused on HBV’s life cycle in order to develop novel treatment strategies. Dr. Doo completed his medical training at UCLA’s Integrated

Training Program in Digestive Diseases, The New York Hospital-Cornell Medical Center, Cornell University Medical College and Stanford University. His research interests include the diagnosis and treatment of chronic viral hepatitis. ∞

# Liver Biopsy Offers Significant Insight for Managing Hepatitis C

Test is Key for HCV Decision-Making but Inappropriate for Most Liver Masses

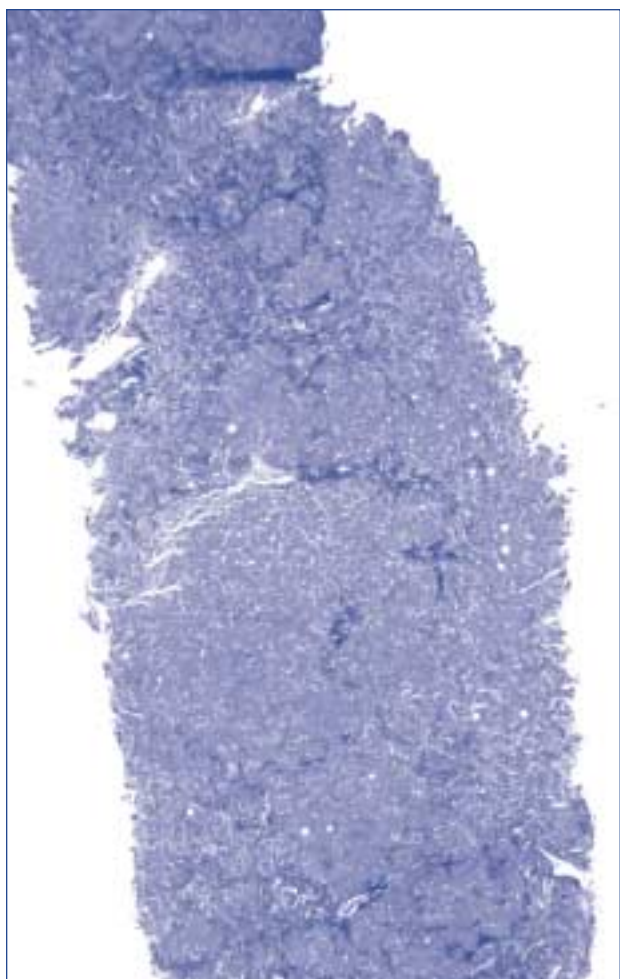
By Adil “Ed” Wakil, M.D. and Laura Miyashita

Liver biopsy is an integral part of hepatology in diagnosing, managing and staging many types of liver disease. From a pathologist’s viewpoint, a liver biopsy serves to:

- confirm diagnosis
- assess severity of inflammation and fibrosis
- assess need for therapeutic intervention and hepatoma screening
- evaluate possible concomitant disease

In cases of a liver mass, important caveats apply, especially if the mass is associated with underlying hepatitis B, C, or hemochromatosis. “Given the high incidence of hepatomas with these diseases and the demonstrated risk of spread due to biopsy, we predominantly rely on imaging and AFP levels to make a diagnosis and assist in management,” says Ed Wakil, M.D., associate medical director of California Pacific’s Liver Disease & Transplant Program. He adds, “A Liver Center should carefully assess these patients for surgical and transplant options before one considers chemotherapy or other modalities.”

For suspicious lesions, California Pacific’s team performs a metastatic work-up consisting of chest, abdomen and pelvic CT scans, and a bone scan. Then a decision is made on how to best manage the lesion, with input from the hepatologist, surgeon, oncologist and radiologist.



Stage 3 fibrosis shown with trichrome stain illustrates a patient highly likely to develop cirrhosis.

## Biopsy in HCV Patients

For hepatitis C (HCV), liver biopsy does not often play a role in diagnosis but rather serves as a tool for patient management and decision-making. In the majority of patients, the Liver Team strongly supports liver biopsy for managing hepatitis C. Exceptions include patients who have clear contraindications to therapy or obvious end-stage disease.

“Over the past 10 years, we have learned much about HCV’s natural history and key risk factors that influence the rate of fibrosis,” says Wakil. These factors include alcohol use, age at acquisition, infection duration, immunosuppression (i.e. HIV coinfection, chronic steroid use, etc.), and possibly gender. By analyzing the patient’s history to determine risk factors for acquisition, one can obtain a probable duration of infection. The liver biopsy results then provide important staging information based on the fibrosis score. With the Metavir system, fibrosis is staged as:

- F0 – normal,
- F1 – portal expansion
- F2 – periportal expansion
- F3 – bridging fibrosis
- F4 – cirrhosis

For most HCV patients, the treatment goal is viral eradication and prevention of cirrhosis and its complications. By knowing the disease stage and estimated duration, one can characterize the patient as either a “slow or rapid fibroser” and assess his or her risk of developing cirrhosis in the near future. This pivotal

## Benefits of Performing a Biopsy for HCV

- Prognostic information: stage and grade of liver damage
- Vital information for fully informed and individualized treatment decisions
- Risk vs. benefit ratio for therapy
- Assists in management decisions once serious side effects occur
- Confirms diagnosis and rules out others

information then helps in deciding whether to proceed with treatment and in prioritizing HCV with other medical problems such as heart disease, tobacco use and diabetes.

“Biopsy results also help us determine how aggressively to support a patient through a difficult and long treatment course with interferon,” says Wakil. He explains, “We want a fully informed patient who can consent to treatment with detailed knowledge of their individual prognosis and priority of liver disease in relation to comorbid conditions and the risks, benefits and cost of therapy.”

For patients who can defer treatment for several years due to the biopsy results, they benefit by avoiding potentially dangerous and expensive therapy with the high likelihood of obtaining more effective, safer therapy in the near future. “If one day we are successful at designing medications that provide the ‘magic bullet’ against HCV, then liver biopsy will no longer be needed,” says Wakil. “But for now, we still have a long way to go.” ∞

## SURVEILLANCE, continued from page 1

improve tumor detection. According to Bonacini, “Screening for specific HCC proteins has been facilitated by proteomics, a key technology that includes proteome analyses. This analysis of proteins expressed via in vitro liver cells offers the hope of earlier and more specific diagnosis of HCC.”

For more information on diagnostic tools or treatment for liver cancer—or to refer patients, call our Specialty Referral Program at 1 (888) 637-2762. ∞

## Recommended HCC surveillance and frequency

Any cirrhosis	U.S., AFP twice a year
HBsAg+, greater than age 35	U.S., AFP yearly
HBsAg with family history of HCC	U.S., AFP yearly
Hemochromatosis	U.S., AFP twice a year
Alfa-1-antitrypsin	U.S., AFP twice a year

U.S.=ultrasound; AFP=alphafetoprotein test

# Research Uncovers New Therapies for Treating Liver Cancer

Options Help Inhibit Tumor Growth

By Robert Gish, M.D. and Laura Miyashita

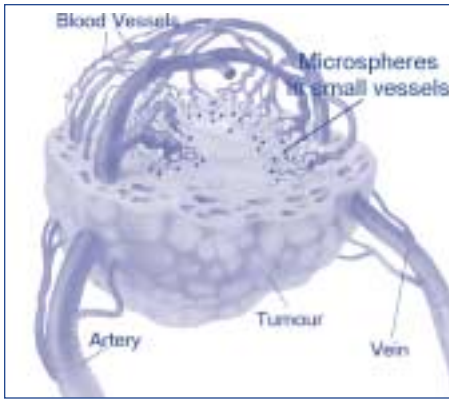


Illustration of radioactive microspheres halting tumor growth via the blood supply.

New options for better managing liver tumors continue to evolve, with research efforts focusing on masses caused by metastatic disease from the colon to the liver. More than 60,000 patients are diagnosed each year with liver tumors that have originated in the colon, from known or suspected colon cancer. Management options for metastatic disease include:

- Embolization
- Cryosurgery
- Radiofrequency and cryoablation
- Hepatic arterial pumps
- Chemotherapy (either direct infusion and/or chemotherapy combined with radiation)

In addition to these options, the following are other newly approved or investigational therapies.

## Radioactive Microspheres

Recently approved by the U.S. Food and Drug Administration (FDA), Yttrium 111 radioactive microspheres offer radioembolization therapy for liver tumors. Used either alone or in combination with systemic chemotherapy, Yttrium 111 can be a precursor to surgical resection if the tumor is too large. The radioactive microspheres are injected to halt tumor growth via the blood supply, thereby enabling subsequent surgical removal once the

tumor size decreases. This new technique is also being explored as a tool for treating primary liver cancer.

## Thymosin Alpha-1

Immunotherapy for liver cancer now includes the use of thymosin alpha-1, an immune cell stimulating agent that also helps prevent the vascular proliferation response required for tumor growth. California Pacific has initiated a clinical research study to determine any benefits of adding thymosin injections to standard chemoembolization. This randomized trial is available for patients who are not candidates for liver transplantation.

## Thymitaq

An option for patients who are not able to undergo liver surgery or direct hepatic treatment is a medication called Thymitaq. This medication inhibits tumor cell metabolism and may have strong growth inhibition on liver cancer. California Pacific's Liver and GI Research Program is conducting a Phase III trial to determine if this medication is better than standard therapies such as intravenous adriamycin.

For details on our clinical research studies, visit [www.cpmc.org/liver](http://www.cpmc.org/liver) and select "Research/Trials" or call (415) 600-1100. ∞



Radioactive microspheres deliver high radiation doses to tumors within the liver.



## Liver Disease Management and Transplant Program

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