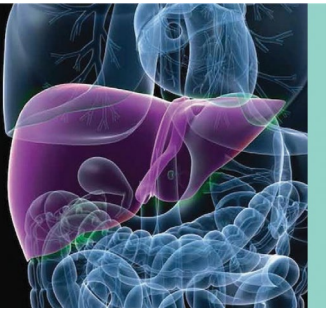# Imaging and Biomarker Approaches to HCC Surveillance

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Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related mortality, with approximately 800,000 deaths worldwide and 27,000 deaths in the United States annually. Its 5-year survival rate remains less than 20%, in part related to the majority of patients presenting beyond an early stage.[1] Professional societies, including the American Association for the Study of Liver Diseases, recommend semiannual surveillance using abdominal ultrasound with or without alpha-fetoprotein (AFP) among at-risk patients to identify HCC at an early stage, when curative options are available (Fig. 1). Herein, we review available and emerging imaging modalities and biomarkers that can be used for HCC surveillance.

IMAGING

Abdominal ultrasound, the current imaging cornerstone for HCC surveillance, has several advantages, including being noninvasive, inexpensive, and safe without risk for contrast or radiation exposure. Ultrasound-based surveillance has been shown to reduce mortality by 37% in patients with chronic hepatitis B (level I data), while several cohort studies have shown a consistent association with improved curative treatment and overall survival in patients with cirrhosis, even after adjusting for lead time and length time biases (level II data).[2,3] However, ultrasound is operator dependent with highly variable sensitivity between providers and centers, and has a pooled sensitivity of only 45% for detecting HCC at an early stage.[4] False-positive or indeterminate results also occur in up to 20% of patients and often lead to unnecessary diagnostic imaging.[5] Ultrasound visualization and effectiveness may be further lower in patients with obesity and nonviral cirrhosis—populations that are increasingly common in clinical practice.[6] Finally, ultrasound-based surveillance often requires a separate appointment, with barriers such as transportation and scheduling, which can reduce utilization and negatively impact surveillance effectiveness.[7]

Given growing recognition of these limitations with ultrasound-based surveillance, there is increasing use of cross-sectional imaging for surveillance in clinical practice. Although a computed tomography–based surveillance strategy is likely not feasible given radiation exposure

Identification of high risk population that includes patients with:
1. Cirrhosis of any etiology
2. Chronic Hepatitis B and
- Asian males age ≥ 40 years
- Asian females age ≥ 50 years
- African males or females at a younger age
- Family history of HCC

Semi-annual Hepatocelluar Carcinoma Surveillance

Liver Ultrasound

+/-

AFP Measurement

FIG 1   Current HCC surveillance strategy.

Hepatocellular Carcimoa Biomarkers

Biochemical Biomarkers

- AFP
- AFP-L3
- Des-gamma carboxyprothombin (DCP)
- Osteopontin
- Dikkopf 1
- Glypican 3 (GPC3)
- Golgi protein 73
- Squamous cell carcinoma antigen
- Fucosylated Glycoproteins
- Glycosylated haptoglobin and other glycosylated proteins

Biomarker Panels

GALAD Score
- Gender
- Age
- AFP
- AFP-L3
- Des-gamma carboxyprothombin (DCP)

HCC Early Detection Screening
- Age
- AFP
- Rate of AFP change
- Alanine aminotransferase
- Platelet count

Kininogen-Based Algorithm
- Age
- Log AFP
- Gender
- Alkaline phosphate
- Alanine aminotransferase
- Fucosylated kininogen

Genomic Biomarkers

Micro RNA

Methylated DNA patterns

Driver Mutations in Cell free DNA
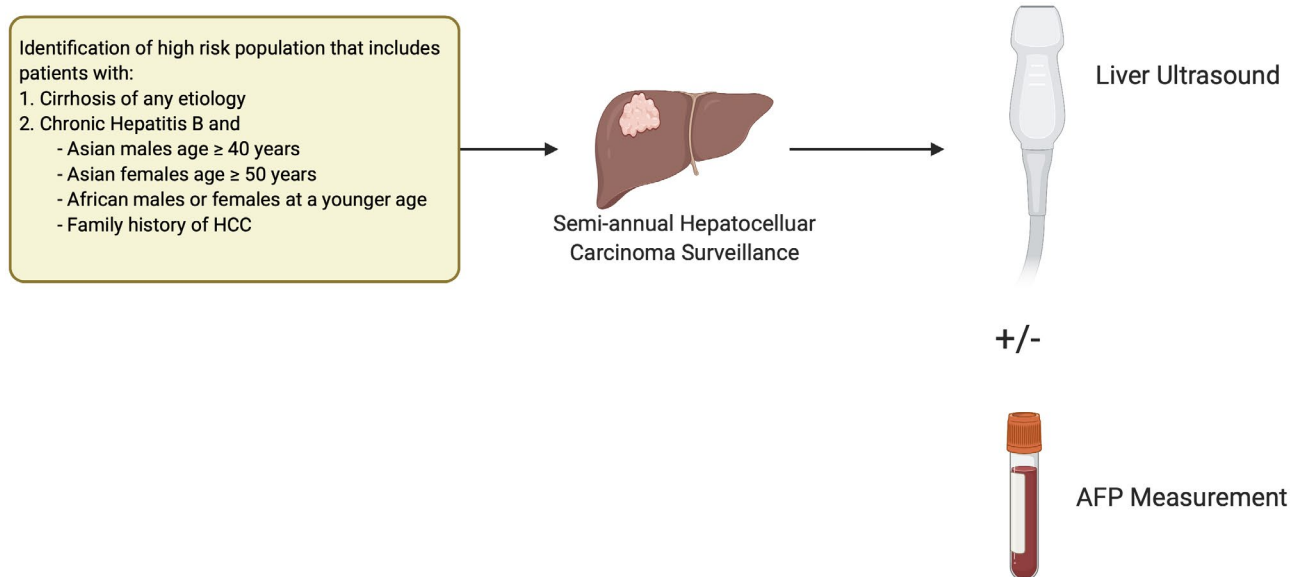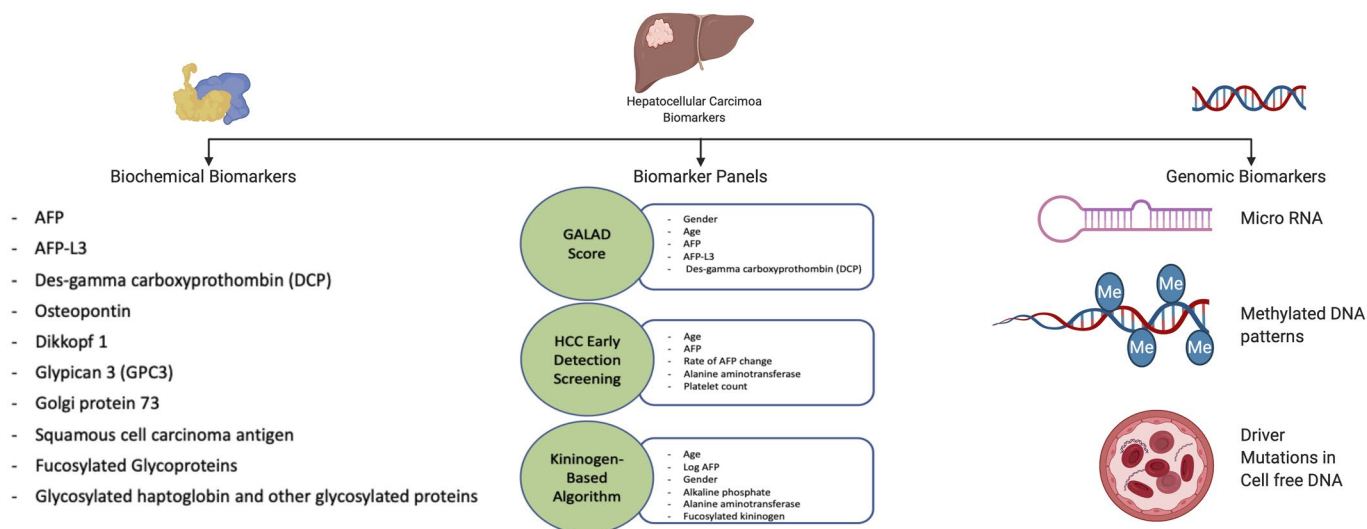
FIG 2   Potential biomarkers for HCC surveillance.

and risk for contrast injury, a magnetic resonance imaging (MRI)-based strategy would not have these same limitations. A cohort study from South Korea compared MRI- and ultrasound-based surveillance in a cohort of 407 patients with cirrhosis and found MRI had significantly higher sensitivity for early HCC detection (85.7% versus 26.2%) with similar specificity (97.0% versus 94.4%).[8] Although promising, there are remaining concerns about cost-effectiveness and lack of confirmatory data in Western non-hepatitis B patient populations. Further, there are concerns about access, particularly in areas of the country with more limited radiological capacity. Case-control studies have found abbreviated MRI protocols, which select specific MRI sequences to decrease in-scanner time from 45 to 15 minutes, may address some of these concerns while preserving high sensitivity for early HCC detection; however, early promising data need to be confirmed in cohort studies.

BIOMARKERS

In addition to alternative imaging modalities, there is also increasing interest in blood-based surveillance biomarkers (Fig. 2). Currently, AFP is the only biomarker that has undergone all five phases of biomarker evaluation (Table 1) and is the most commonly used biomarker in practice. Although AFP is inexpensive, objective, and widely available, its limited sensitivity to detect early-stage HCC and false-positive results in the setting of active viral hepatitis have historically hampered enthusiasm. However, AFP appears to be of benefit when used with ultrasound, with a meta-analysis demonstrating increased sensitivity for early HCC detection from 45% using ultrasound alone to 63% with the two tests in combination.[4] Further, AFP false-positive results appear to be less common in nonviral cirrhosis, and physical harms from false-positive results appear to be mitigated in practice by providers using longitudinal changes when interpreting AFP values instead of relying on the traditional single-threshold measurement of 20 ng/mL.[5]

Several new blood-based biomarkers, such as lectin-bound AFP (AFP-L3%) and des-gamma-carboxyprothrombin (DCP), are also under investigation (Fig. 2). Most of these biomarkers have been evaluated in only phase II (case-control) biomarker studies and still require validation in phase III and phase IV (cohort) studies.[9] The maturation of large cohort studies, such as Early Detection Research Network HCC Early Detection Strategy Study and Texas HCC Consortium, should facilitate phase III evaluation of several biomarkers in the near future. Current data suggest that single biomarkers may not be sufficient for early HCC detection, likely related to HCC heterogeneity. Therefore, there has been increased interest in biomarker panels, combining several biomarkers with or without clinical variables. For example, GALAD is a panel that combines gender, age, AFP-L3%, AFP, and DCP, which has been evaluated in a large multinational case-control study with a sensitivity of 60% to 80% for detecting early-stage HCC.[10]

With advances in genomics, there also has been increased identification of dysregulated nucleic acids that can also serve as surveillance biomarkers. Circulating noncoding RNAs or microRNAs (miRNAs), such as miRNA-21 and miRNA-199a, have been identified in patients with early HCC.[9] Similarly, DNA abnormalities isolated from circulating tumor cells and quantitative analysis of cell-free DNA have shown moderate sensitivity and accuracy for detecting HCC.[9] A methylated DNA marker panel was recently shown to have promising accuracy in a phase II biomarker study, with sensitivity and specificity for early HCC detection of 70% and 89%, respectively.[11] However, these biomarkers also still require validation in large cohort studies using standardized processing techniques and cutoffs.

SUMMARY

HCC surveillance should be performed as recommended in patients with chronic hepatitis B and patients with cirrhosis to reduce HCC-related mortality. Semiannual abdominal ultrasound and AFP is currently the best strategy to maximize early detection; however, this strategy misses more than one-third of HCCs at an early stage, highlighting the need for better tests. MRI-based imaging strategies may increase sensitivity for early HCC detection, although there are potential concerns about cost-effectiveness and radiological capacity. In parallel, there are several promising blood-based protein and genomic biomarker panels that have shown high sensitivity for early HCC detection in early case-control studies. These biomarkers still require validation in large cohort studies but have potential to truly transform how we perform HCC surveillance among at-risk patients.

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TABLE 1. PHASES OF BIOMARKER VALIDATION FOR EARLY DETECTION

Phase of Development	Definition
I	Identify potential biomarkers in a preclinical setting.
II	Assess the ability of the assay to distinguish between cases and controls.
III	Analyze the ability of the assay to analyze preclinical disease.
IV	Assess operating characteristics of biomarker-based screening in the target population.
V	Assess the impact of screening on cancer mortality.

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