



## **Biomarker-Guided and Imaging-Based Evaluation of Treatment Response in Hepatocellular Carcinoma: Current Evidence and Future Perspectives**

**Amany Mohammed Ibrahim<sup>1</sup>, Fady Maher Wadea<sup>1</sup>, Sameh Saber Bayoumi<sup>2</sup>, Marwa Mohammed Esawy<sup>3</sup>, Heba Sayed Ahmed Abdel Hamid Elsayed<sup>1</sup>**

1 Internal Medicine Department, Faculty of Medicine, Zagazig University. Egypt

2 Radiology Department, Faculty of Medicine, Zagazig University. Egypt

3 Clinical Pathology Department, Faculty of Medicine, Zagazig University. Egypt

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### ***Abstract***

**Background:** Hepatocellular carcinoma (HCC) remains a major global health challenge as the most common primary liver malignancy and a leading cause of cancer-related death. Despite advances in systemic therapies and locoregional approaches, evaluating treatment response remains a critical obstacle in clinical practice. Conventional imaging-based criteria, such as RECIST, are often insufficient due to the unique biological features of HCC, including its vascularity and necrotic changes after therapy. Similarly, reliance on serum alpha-fetoprotein (AFP) alone has proven inadequate due to variable sensitivity and specificity. In this context, biomarkers and imaging modalities have evolved as complementary strategies for assessing therapeutic outcomes. Novel biomarkers such as des- $\gamma$ -carboxy prothrombin (DCP), AFP-L3, and circulating tumor DNA offer potential advantages for early detection of treatment response and resistance. Moreover, liquid biopsy technologies and omics-based markers are providing new insights into tumor heterogeneity and disease dynamics. In parallel, advances in radiology—including multiphase CT, hepatobiliary MRI, and functional imaging—have improved detection of viable tumor tissue and evaluation of locoregional therapy efficacy. Importantly, integration of biomarker data with imaging criteria has emerged as a promising approach to overcome limitations of each modality. Predictive models that combine serum markers with radiological findings may enhance precision in response assessment and allow earlier identification of treatment failure. Such synergy is particularly relevant in the era of immunotherapy and targeted agents, where unconventional response patterns challenge traditional evaluation systems. This review summarizes current evidence regarding biomarker-guided and imaging-based evaluation of treatment response in HCC. We highlight the clinical utility of established and emerging biomarkers, discuss the evolving role of radiology, and explore future directions such as radiogenomics and multi-omics integration. By synthesizing these domains, we aim to provide a comprehensive perspective on how biomarker and imaging-based strategies can be harnessed to optimize patient monitoring and support personalized treatment approaches in HCC.

**Keywords:** *Biomarker-Guided, Imaging, Hepatocellular Carcinoma.*



## Introduction

Hepatocellular carcinoma (HCC) accounts for nearly 90% of primary liver cancers and represents a global health burden, with rising incidence and high mortality rates worldwide. The prognosis of HCC remains poor due to late diagnosis, frequent recurrence, and limited curative options. Advances in systemic treatments, including tyrosine kinase inhibitors and immune checkpoint inhibitors, alongside locoregional therapies such as transarterial chemoembolization (TACE) and radiofrequency ablation, have expanded therapeutic opportunities. However, accurate evaluation of treatment response continues to be one of the most pressing challenges in clinical hepatology and oncology [1].

Traditional assessment methods rely on radiological measurements of tumor size, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST). While valuable in many cancers, these criteria fall short in HCC due to the tumor's unique vascular characteristics and the impact of locoregional therapies, which may induce necrosis without reducing tumor volume. Similarly, serum alpha-fetoprotein (AFP), historically used as a biomarker, lacks sufficient sensitivity and specificity to reliably reflect therapeutic outcomes [2]. This dual limitation underscores the need for more refined approaches.

The emergence of novel biomarkers, including des- $\gamma$ -carboxy prothrombin (DCP) and circulating tumor DNA, along with innovations in advanced imaging such as diffusion-weighted MRI and radiomics, offers new opportunities for precision monitoring. Yet, each modality carries inherent constraints, necessitating a multimodal approach that integrates biochemical and imaging markers. This combined strategy holds promise for earlier detection of therapeutic response, prediction of resistance, and improved patient stratification [3].

The aim of this review is to synthesize current evidence on biomarker-guided and imaging-based evaluation of treatment response in HCC. We explore established and emerging biomarkers, critically examine radiological assessment methods with a focus on practical applicability rather than technical depth, and highlight the potential of integrated approaches. By addressing the existing research gap, this article seeks to provide clinicians and researchers with a comprehensive overview of evolving strategies to improve therapeutic monitoring and ultimately patient outcomes in HCC.

### **Biomarkers in Evaluating Locoregional Therapy Response**

Alpha-fetoprotein (AFP) has historically been the most widely used serum biomarker in hepatocellular carcinoma. In the context of locoregional therapy, trends in AFP levels provide valuable information about treatment response. A significant decline in AFP after transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) has been associated with improved survival and reduced recurrence rates, while persistently elevated or rising AFP suggests incomplete ablation or early progression [4]. The AFP-L3 isoform, representing a glycosylated fraction of AFP, has shown higher specificity for malignant hepatocytes and correlates with more aggressive disease biology. Its persistence after ablation or embolization has been linked to higher recurrence risks, highlighting its potential utility in structured follow-up strategies [5].

Des- $\gamma$ -carboxy prothrombin (DCP), also known as protein induced by vitamin K absence or antagonist-II (PIVKA-II), has gained attention as a clinically relevant biomarker. Elevated levels are strongly correlated with microvascular invasion, tumor progression, and poor prognosis. Following locoregional therapies, normalization of DCP has been associated with better disease control, while persistent or rising levels suggest residual viable tumor [6]. Compared to AFP, DCP may provide a more reliable indication of vascular involvement and recurrence after embolization, which is particularly useful in patients treated with TACE or radioembolization [7].

Recent advances in liquid biopsy techniques have introduced circulating tumor DNA (ctDNA) as a promising monitoring tool after locoregional therapy. Detection of ctDNA fragments carrying tumor-specific mutations can reflect minimal residual disease even when imaging findings remain inconclusive. Several studies have shown that ctDNA clearance after ablation or embolization correlates with complete response, while persistence of tumor-specific mutations predicts recurrence months before radiologic



evidence becomes apparent [8]. Beyond recurrence detection, liquid biopsy also provides dynamic insights into clonal evolution and treatment resistance, suggesting that it could complement imaging during repeated cycles of locoregional intervention [9].

Systemic inflammatory and immune markers have also been investigated as prognostic tools in patients undergoing locoregional therapy. Parameters such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and interleukin-6 (IL-6) reflect systemic inflammation, which plays a key role in tumor progression and treatment response. Elevated baseline or post-procedure NLR has been consistently associated with poorer survival after TACE, while high post-TACE CRP levels have been correlated with treatment-related liver injury and worse prognosis [10]. Although these markers are not specific to hepatocellular carcinoma, they provide useful adjunctive information, particularly when interpreted alongside AFP trends and radiological findings [11].

Beyond conventional biomarkers, ongoing research is exploring the role of multi-omics approaches in improving response evaluation after locoregional therapy. Genomic, proteomic, and metabolomic profiles are being studied for their ability to distinguish responders from non-responders to embolization or ablation. Proteomic signatures, for instance, have shown potential in stratifying patients according to treatment efficacy, while metabolomic alterations in bile acid and lipid profiles have been linked to recurrence patterns following ablation [12]. Although these omics-based biomarkers remain experimental, integrating them with clinical and imaging data may eventually enable more precise and personalized follow-up strategies. Such approaches could facilitate earlier recognition of treatment failure and allow timely adaptation of therapeutic sequencing [13].

#### **Radiological Evaluation After Locoregional Therapy**

Radiological imaging remains central to evaluating hepatocellular carcinoma after locoregional therapy. Traditionally, treatment response has been assessed using the Response Evaluation Criteria in Solid Tumors (RECIST), which are based on measurements of tumor size. However, in the setting of TACE, RFA, or radioembolization, tumor shrinkage may not accurately reflect therapeutic efficacy. These procedures often induce tumor necrosis without significant size reduction, making RECIST insensitive for detecting viable tumor tissue. Consequently, reliance on size-based assessment alone may lead to misclassification of response and delays in recognizing treatment failure [14].

To overcome these shortcomings, modified RECIST (mRECIST) and guidelines from the European Association for the Study of the Liver (EASL) have been introduced. These criteria focus on evaluating viable tumor tissue as defined by contrast enhancement in arterial phases rather than absolute lesion size. The assessment of arterial enhancement provides a more reliable surrogate for tumor viability, particularly after embolization or ablation, where necrosis is a primary therapeutic goal. Several studies have validated the superiority of mRECIST over conventional RECIST in predicting overall survival and recurrence in patients undergoing TACE, establishing it as the preferred standard in clinical practice [15].

Cross-sectional imaging modalities such as multiphasic computed tomography (CT) and magnetic resonance imaging (MRI) play a pivotal role in monitoring response after locoregional therapy. CT remains widely available and reliable in detecting residual enhancing tumor tissue, though its sensitivity may be limited in small lesions or in patients with poor liver function. MRI offers greater soft-tissue contrast and functional sequences such as diffusion-weighted imaging (DWI), which can help identify early necrosis and residual viable tissue with greater sensitivity. The use of hepatobiliary-specific contrast agents in MRI further improves detection of small intrahepatic recurrences, enhancing its role in surveillance following ablation or embolization [16].

Emerging functional and advanced imaging approaches are gradually reshaping response assessment. Positron emission tomography (PET), while limited by variable uptake in HCC, has been explored for its potential to detect aggressive disease biology and extrahepatic progression. Radiomics and artificial intelligence-driven models, applied to CT and MRI datasets, are being investigated for their ability to quantify tumor heterogeneity and predict treatment outcomes beyond visual interpretation. Although still in the research phase, these tools may eventually complement conventional imaging by providing predictive



biomarkers embedded within radiologic data, thereby refining follow-up strategies after locoregional therapy [17].

### **Integration of Biomarkers and Imaging in Follow-Up**

The integration of biomarkers and imaging has become increasingly important in the follow-up of hepatocellular carcinoma treated with locoregional therapies. While radiological evaluation provides an anatomic and functional assessment of the treated lesion, biomarkers offer a systemic reflection of tumor activity and residual disease. Used together, these modalities can overcome the limitations of relying on a single assessment tool. For instance, when imaging reveals equivocal enhancement patterns after embolization, concurrent declines in AFP or DCP levels may support classification as a treatment response. Conversely, if biomarker levels remain persistently elevated despite imaging appearances of complete necrosis, clinicians may be prompted to intensify surveillance for residual disease or occult metastasis [18]. A common clinical challenge is the mismatch between biomarker trends and imaging findings. Cases have been documented where patients demonstrate radiological evidence of complete response after TACE, yet AFP or DCP levels remain elevated, later proving to predict recurrence within months. Similarly, patients with early biomarker normalization may still harbor viable microscopic disease undetectable on imaging. These discrepancies highlight the complementary nature of biomarkers and radiology. Rather than being interpreted in isolation, integrating both sources of information provides a more nuanced picture of treatment efficacy and recurrence risk [19].

The combination of biomarkers and imaging has also been applied to the development of predictive models and nomograms for clinical decision-making. Several prognostic scoring systems now incorporate AFP kinetics alongside mRECIST-based imaging criteria to stratify patients after TACE into risk categories for recurrence and survival. Such models can guide treatment sequencing, identifying patients who would benefit from repeated embolization versus those requiring early transition to systemic therapy. Incorporating ctDNA or novel inflammatory indices into these algorithms may further refine their predictive accuracy, advancing the goal of personalized follow-up strategies [20].

In the era of precision medicine, integration of biomarkers with imaging also holds promise in monitoring emerging therapeutic approaches such as combination locoregional and immunotherapy regimens. Unconventional response patterns, including pseudo-progression after immunomodulation, complicate interpretation of imaging alone. Biomarkers, particularly immune-related signatures and liquid biopsy-derived ctDNA, may serve as adjunctive indicators of true disease activity in these contexts. This synergistic approach not only improves the accuracy of treatment response assessment but also accelerates the identification of patients at high risk of treatment failure, enabling timely intervention and potentially better outcomes [21].

### **Challenges and Limitations**

Despite significant advances in both biomarker discovery and radiological evaluation, several challenges limit their widespread use in the follow-up of hepatocellular carcinoma treated with locoregional therapies. A major obstacle is the lack of standardization in biomarker measurement and interpretation. AFP and DCP thresholds vary across institutions, and no consensus exists on what constitutes a clinically meaningful decline after embolization or ablation. Similarly, while ctDNA and liquid biopsy approaches are highly promising, their use remains limited by technical variability, high cost, and lack of validated cut-off values for guiding treatment decisions [22].

Radiological assessment also faces important limitations. Even with the adoption of mRECIST and EASL criteria, interpretation of imaging after locoregional therapy can be challenging due to post-procedure changes such as edema, hemorrhage, or inflammatory enhancement, which may mimic viable tumor. Inter-observer variability among radiologists further complicates consistent classification of response. Moreover, the reliance on arterial enhancement as a surrogate for viability may not always capture microscopic residual disease, leading to false-negative assessments that delay recognition of recurrence [23].

Another limitation lies in the heterogeneity of hepatocellular carcinoma itself. Tumor biology varies widely across patients, and biomarker kinetics may not always reflect treatment efficacy in a uniform manner. For example, a subset of patients with normal baseline AFP or DCP cannot be monitored effectively using these



markers, necessitating alternative strategies. Similarly, inflammatory markers such as NLR and CRP lack specificity, as they can be influenced by concurrent infections, comorbidities, or treatment-related hepatic injury, thereby limiting their reliability when interpreted in isolation [24].

Finally, issues of accessibility and cost hinder the integration of advanced monitoring approaches into routine practice. While MRI with hepatobiliary contrast agents and liquid biopsy assays offer superior sensitivity, their availability is often restricted to tertiary centers and remains economically unfeasible in resource-limited settings. This creates disparities in the quality of follow-up care across different healthcare systems. Addressing these challenges will require multicenter validation studies, harmonization of biomarker assays, and development of cost-effective imaging and molecular tools to ensure equitable application of these strategies in clinical practice [25].

### **Conclusion**

The evaluation of treatment response in hepatocellular carcinoma following locoregional therapy remains a complex but critically important aspect of patient management. Neither biomarkers nor imaging alone provide a sufficiently comprehensive picture of therapeutic efficacy. Biomarkers such as AFP, DCP, and emerging liquid biopsy approaches offer dynamic systemic insights into tumor biology, while imaging provides essential information on local tumor viability and anatomic changes. When used in combination, these modalities create a more reliable framework for assessing outcomes, detecting recurrence, and guiding subsequent treatment strategies.

Despite clear progress, significant challenges persist. Variability in biomarker interpretation, limitations of imaging criteria, tumor heterogeneity, and disparities in access to advanced technologies continue to hinder universal implementation. Nonetheless, the integration of biomarkers and radiology represents a major step toward precision monitoring in hepatocellular carcinoma. As research continues to refine these tools and explore novel multi-omics and radiogenomic approaches, the goal of individualized and accurate follow-up after locoregional therapy is becoming increasingly attainable. Ultimately, adopting combined assessment strategies has the potential to improve clinical decision-making, optimize treatment sequencing, and enhance long-term outcomes for patients with this challenging disease.

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