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Emerging Biomarkers in AFP-Low HCC: Evaluating the Role of Fibroblast Growth Factor 19 after Locoregional Treatment

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ABSTRACT

***Background*:** Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies worldwide and remains a leading cause of cancer-related mortality. Locoregional therapies, including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave ablation, and radioembolization, form the backbone of treatment for patients who are not candidates for surgical resection or transplantation. Accurate assessment of therapeutic response and long-term follow-up are essential in this setting, as recurrence rates remain high and survival outcomes depend on early recognition of residual or recurrent disease. Traditionally, alpha-fetoprotein (AFP) has served as the primary biomarker in HCC surveillance. However, up to 40% of patients present with AFP-low or AFP-negative tumors, limiting the utility of this marker and creating a significant gap in clinical practice.

Fibroblast growth factor 19 (FGF19) has recently emerged as a promising candidate biomarker to address this unmet need. Physiologically involved in bile acid metabolism through FGFR4/β-Klotho signaling, FGF19 plays a critical role in hepatocyte proliferation and metabolic regulation. Aberrant overexpression of FGF19, often driven by gene amplification, has been implicated in hepatocarcinogenesis through activation of oncogenic signaling pathways such as MAPK and STAT3. Elevated serum and tissue levels of FGF19 have been documented in patients with HCC and are associated with larger tumor size, vascular invasion, and poorer prognosis. Importantly, several studies suggest that in AFP-low HCC, dynamic changes in FGF19 levels may correlate with treatment response after locoregional therapy, providing information that imaging alone may fail to capture.

The integration of FGF19 with radiological assessment offers a potential paradigm shift in surveillance. While modified RECIST (mRECIST) criteria and contrast-enhanced CT or MRI remain the gold standard for evaluating residual tumor viability, post-treatment changes frequently complicate interpretation. The adjunctive use of FGF19 may enhance diagnostic accuracy, resolve equivocal cases, and allow earlier detection of recurrence. Nonetheless, challenges remain, including assay variability, confounding effects of underlying liver disease, and limited validation in large cohorts.

This review examines the biological role of FGF19 in hepatocarcinogenesis, its emerging utility as a biomarker in AFP-low HCC, and its potential integration with imaging-based follow-up after locoregional therapy. By addressing a critical gap in post-treatment surveillance, the evaluation of FGF19 may pave the way toward more precise and individualized monitoring strategies in this challenging patient population

Keywords: AFP, Fibroblast Growth Factor 19, HCC

INTRODUCTION

Hepatocellular carcinoma accounts for approximately 90% of primary liver cancers and represents the sixth most common malignancy and the third leading cause of cancer-related death globally [1]. The disease burden is expected to rise further due to the persistence of chronic hepatitis B infection in endemic regions, the increasing prevalence of metabolic-associated steatotic liver disease (MASLD), and alcohol-related liver disease. For patients who are not candidates for surgical resection or transplantation, locoregional therapies such as TACE, RFA, microwave ablation, and radioembolization remain the cornerstone of treatment. These interventions can prolong survival, achieve local tumor control, and, in some cases, provide a bridge to curative options. However, the long-term efficacy of these approaches is often undermined by high recurrence rates, necessitating close surveillance and timely recognition of treatment failure [2].

Accurate monitoring after locoregional therapy is essential yet challenging. Radiological assessment remains the gold standard, with criteria such as RECIST and mRECIST providing standardized approaches to measuring tumor response. However, these size- or enhancement-based systems are limited in their ability to distinguish viable tumor from post-procedural necrosis, edema, or inflammation. Reliance on imaging alone may therefore lead to diagnostic uncertainty, delayed recognition of recurrence, or overtreatment in ambiguous cases. To complement radiology, serum biomarkers have traditionally been used to provide systemic information on tumor activity, with AFP serving as the most widely employed marker in both surveillance and treatment monitoring [3].

The limitations of AFP in clinical practice are well documented. Approximately 30–40% of HCC patients present with low or normal AFP levels despite active disease, and many AFP-negative tumors display aggressive biology and poor outcomes. In these patients, AFP provides little or no value for post-treatment follow-up, leaving clinicians dependent solely on imaging. This subgroup therefore represents a critical unmet need in the management of HCC, underscoring the importance of identifying alternative biomarkers that can aid in treatment response evaluation and surveillance after locoregional therapy [4].

Fibroblast growth factor 19 has emerged as a novel candidate in this regard. Initially recognized as a metabolic regulator of bile acid synthesis, FGF19 has since been implicated in hepatocarcinogenesis through gene amplification and aberrant FGFR4/β-Klotho signaling. Elevated FGF19 levels have been detected in both serum and tumor tissue of HCC patients and are associated with larger tumors, vascular invasion, and early recurrence. Importantly, early evidence suggests that in AFP-low HCC, dynamic changes in serum FGF19 may reflect treatment response after locoregional therapy and predict disease recurrence before radiological evidence becomes apparent [5].

The aim of this review is to comprehensively examine the role of FGF19 as an emerging biomarker in AFP-low HCC following locoregional therapy. We discuss the biological underpinnings of FGF19 in liver carcinogenesis, its current and potential clinical applications in biomarker-guided follow-up, and how it may complement radiological strategies to improve surveillance. By focusing on this specific and challenging subgroup, this article highlights the promise of FGF19 as a step toward more individualized and effective monitoring protocols for HCC.

Biology of FGF19 and Its Role in Hepatocellular Carcinoma

Fibroblast growth factor 19 (FGF19) belongs to the endocrine fibroblast growth factor family, which also includes FGF21 and FGF23. Unlike paracrine FGFs, endocrine FGFs circulate systemically and exert effects on distant organs. Under physiological conditions, FGF19 is secreted by ileal enterocytes in response to bile acid activation of the farnesoid X receptor (FXR). Once released into the portal circulation, FGF19 binds to fibroblast growth factor receptor 4 (FGFR4) on hepatocytes, in conjunction with the co-receptor β-Klotho. This signaling cascade suppresses cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid synthesis, thereby maintaining bile acid and metabolic homeostasis. Beyond its regulatory role in bile acids, FGF19 has effects on hepatocyte proliferation, glycogen synthesis, and lipid metabolism, linking it directly to hepatic growth and energy regulation [6].

In hepatocellular carcinoma, the FGF19–FGFR4 axis is frequently dysregulated. One of the most consistent findings in genomic studies is amplification of the FGF19 locus on chromosome 11q13, a region recurrently altered in HCC. This amplification leads to overproduction of FGF19 protein, which in turn drives constitutive FGFR4 activation independent of bile acid stimulation. The downstream signaling involves multiple oncogenic pathways, including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT, and STAT3. Activation of these cascades results in enhanced cellular proliferation, evasion of apoptosis, angiogenesis, and epithelial-to-mesenchymal transition, all of which contribute to tumor initiation and progression. Importantly, FGF19-driven carcinogenesis is not limited to tumor growth but also fosters a microenvironment conducive to invasion and recurrence [7].

Preclinical studies have provided compelling evidence of the oncogenic potential of FGF19. In mouse models, transgenic overexpression of FGF19 leads to spontaneous development of hepatocellular carcinoma, while pharmacologic blockade of FGFR4 signaling prevents tumor formation and slows progression in established disease. These findings demonstrate that aberrant FGF19 signaling is not merely a marker of disease activity but also a functional driver of hepatocarcinogenesis. Furthermore, experiments have shown that FGF19-overexpressing tumors display resistance to apoptosis and increased angiogenic potential, reinforcing the idea that the FGF19–FGFR4 axis is a critical oncogenic pathway in the liver [8].

Clinical investigations have corroborated these experimental findings. Elevated serum FGF19 levels have been reported in patients with HCC compared to cirrhotic controls, and high tumor tissue expression has been observed in up to 50% of resected HCC specimens. Patients with strong FGF19 expression in tumor tissue are more likely to present with large tumors, microvascular invasion, and advanced tumor stage at diagnosis. Moreover, elevated FGF19 expression has been consistently associated with shorter recurrence-free survival and overall survival, suggesting a prognostic role beyond its biological contribution to tumor growth. Importantly, in AFP-low tumors, FGF19 expression has been shown to capture malignant activity that AFP fails to detect, highlighting its particular relevance in this subgroup [9].

An additional dimension of FGF19 biology is its potential contribution to treatment resistance. Recent studies indicate that activation of the FGF19–FGFR4 axis may reduce sensitivity to systemic therapies such as sorafenib, through sustained activation of MAPK and STAT3 pathways. Similarly, tumors with high FGF19 expression have shown poorer responses to locoregional therapy, likely due to enhanced survival signaling and angiogenesis that facilitate rapid recurrence after embolization or ablation. These observations strengthen the argument that FGF19 is both a biomarker and a therapeutic target. Its dual role

underscores why evaluating FGF19 in the surveillance of AFP-low HCC is both biologically plausible and clinically valuable [10].

FGF19 as a Biomarker in AFP-Low Hepatocellular Carcinoma

Alpha-fetoprotein remains the most widely used serum biomarker in hepatocellular carcinoma, yet its limitations are striking in the AFP-low subgroup. Between 30% and 40% of patients with HCC present with AFP levels below diagnostic thresholds, and up to 15% remain persistently negative even at advanced disease stages [11]. This subset of patients is particularly challenging because AFP cannot provide early warning of recurrence or incomplete response after locoregional therapy. Imaging alone therefore becomes the primary surveillance tool, but post-treatment changes such as necrosis, inflammation, or lipiodol deposition can complicate radiologic interpretation. In this clinical gap, alternative biomarkers are urgently needed to aid follow-up in AFP-low tumors.

FGF19 has emerged as one of the most promising candidates to address this unmet need. Clinical studies have demonstrated that serum FGF19 is frequently elevated in AFP-low HCC patients compared with cirrhotic or hepatitis controls, suggesting it may serve as a sensitive marker of malignant activity independent of AFP [12]. In particular, elevated pre-treatment FGF19 has been associated with aggressive tumor features such as vascular invasion and larger tumor burden, even in patients whose AFP remained normal. These findings position FGF19 as a potential biomarker capable of capturing tumor biology that AFP fails to reflect, thereby expanding the scope of surveillance tools available for AFP-low HCC.

Dynamic changes in serum FGF19 following locoregional therapy may provide further clinical value. In patients treated with TACE or RFA, declining FGF19 levels post-procedure have been correlated with radiological response and prolonged progression-free survival. Conversely, patients with persistently high or rising FGF19 levels despite apparent radiological necrosis frequently develop recurrence within months, highlighting its predictive power. In this way, FGF19 offers the possibility of early detection of residual disease, complementing imaging and supporting more confident therapeutic decision-making [13].

When compared to other non-AFP biomarkers, such as des-γ-carboxy prothrombin (DCP) and AFP-L3, FGF19 appears to offer distinct advantages. DCP has shown prognostic value but is influenced by vitamin K status and anticoagulant therapy, which limits its specificity. AFP-L3 is more specific than AFP, but its sensitivity is restricted, especially in smaller or early-stage tumors. By contrast, FGF19 reflects an oncogenic signaling pathway central to hepatocarcinogenesis, potentially offering both higher biological relevance and prognostic power. This mechanistic connection to tumor biology provides an additional rationale for its use in AFP-low cases where other markers often fall short [14].

Tissue-level studies reinforce the potential of FGF19 as a prognostic marker. Immunohistochemical analysis of resected or ablated HCC specimens has revealed that high intratumoral FGF19 expression is associated with microvascular invasion, higher recurrence rates, and shorter survival. Importantly, this association has been demonstrated in patients with AFP-low tumors, confirming its value in a subgroup often overlooked by conventional biomarkers. Moreover, genomic studies have identified amplification of the 11q13 locus containing the FGF19 gene in a subset of HCC patients, further supporting its role as a driver event and as a marker of poor prognosis [15].

The utility of FGF19 in AFP-low HCC extends beyond diagnosis and prognosis into therapeutic guidance.

By identifying patients with biologically aggressive tumors despite normal AFP, FGF19 testing could help stratify risk and tailor surveillance intensity after locoregional therapy. For instance, patients with high post-treatment FGF19 may benefit from closer radiological follow-up or consideration of adjuvant systemic therapy, while those with declining FGF19 might be managed with standard surveillance intervals. Although large-scale validation is still needed, these findings suggest that FGF19 could become a cornerstone biomarker for post-treatment monitoring in AFP-low hepatocellular carcinoma [16].

Imaging and Biomarker Integration in AFP-Low Hepatocellular Carcinoma

Radiological evaluation remains the cornerstone for assessing treatment response and monitoring recurrence after locoregional therapy in hepatocellular carcinoma. Contrast-enhanced multiphasic computed tomography (CT) and magnetic resonance imaging (MRI) are routinely employed to detect residual viable tumor based on arterial phase enhancement. Modified RECIST (mRECIST) criteria, which emphasize viable tumor rather than size alone, have become the standard in clinical practice. However, in AFP-low patients, where serum markers provide little guidance, imaging often becomes the sole modality for follow-up. This reliance is problematic, as post-procedural changes such as coagulative necrosis, inflammatory hyperemia, or lipiodol deposition after TACE can mimic tumor viability, creating diagnostic ambiguity [17].

The integration of FGF19 with radiological monitoring may provide a more robust framework for follow-up in this challenging subgroup. Rising FGF19 levels in AFP-low patients after TACE or ablation have been shown to precede radiologic evidence of recurrence, suggesting that FGF19 can serve as an early warning signal. Conversely, a decline in FGF19 following therapy supports radiologic evidence of complete necrosis, strengthening confidence in treatment response. Such dual validation could improve diagnostic accuracy, especially in cases where imaging findings are equivocal. By combining the systemic information offered by FGF19 with the anatomical detail of imaging, clinicians may achieve a more comprehensive assessment of treatment outcomes [18].

One of the most valuable contributions of FGF19 integration lies in resolving biomarker–imaging mismatches. For example, when imaging suggests a complete response but FGF19 levels remain elevated, this may indicate microscopic residual disease, prompting closer surveillance or early retreatment. Conversely, if radiological enhancement raises suspicion of recurrence but FGF19 levels are stable or declining, a more conservative approach might be warranted to avoid unnecessary interventions. Such complementary interpretation mirrors the combined use of AFP and imaging in AFP-positive patients, but extends this paradigm to AFP-low disease, where the need is greatest [19].

FGF19 may also play a role in risk stratification models that integrate biomarkers with imaging features. Several prognostic nomograms for HCC already combine AFP kinetics with radiological criteria to predict survival after TACE. In AFP-low patients, FGF19 could serve as a surrogate in these models, enabling risk categorization and guiding surveillance intensity. Emerging data suggest that combining FGF19 trends with imaging-based criteria improves predictive accuracy for recurrence compared to imaging alone. This integrated approach aligns with the broader trend in oncology toward multimodal assessment, where molecular and radiological biomarkers are analyzed together to capture both biological activity and anatomical disease burden [20].

Beyond routine surveillance, integration of FGF19 with imaging may prove particularly relevant in the setting of novel therapeutic strategies that combine locoregional and systemic therapies. Immunotherapy, for example, can produce atypical radiologic response patterns such as pseudo-progression, which may confound mRECIST interpretation. In AFP-low patients receiving such combination regimens, FGF19 could help clarify whether radiological changes reflect true progression or immune-mediated effects. While evidence is still limited, these possibilities underscore the potential of FGF19 to complement imaging across a spectrum of clinical scenarios in AFP-low hepatocellular carcinoma [21].

Future Perspectives

The role of FGF19 as a biomarker in AFP-low hepatocellular carcinoma is still in its early stages, but the biological rationale and preliminary clinical data are compelling. Future research is expected to focus on validating FGF19 in larger, multicenter cohorts to establish standardized thresholds for clinical decision-making. Prospective studies are particularly needed to determine whether dynamic changes in FGF19 after locoregional therapy can reliably predict recurrence across diverse populations. In addition, efforts should aim to integrate FGF19 into existing surveillance algorithms to compare its utility against established markers such as DCP and AFP-L3 in AFP-low cases [22].

Therapeutic implications also add to the promise of FGF19. Given that FGF19 acts as a driver of hepatocarcinogenesis through FGFR4 activation, targeted therapies against this pathway are under active investigation. Selective FGFR4 inhibitors such as fisogatinib (BLU-554) and H3B-6527 have demonstrated early antitumor activity in FGF19-positive HCC patients. The dual role of FGF19 as both a biomarker and therapeutic target raises the possibility of a biomarker-driven treatment paradigm in AFP-low disease, where identifying patients with high FGF19 expression could guide enrollment into targeted therapy trials while also improving surveillance [23].

The integration of FGF19 into multi-omics and radiogenomics approaches represents another important frontier. Combining genomic, proteomic, and metabolomic data with imaging biomarkers could provide highly individualized monitoring strategies. In this context, FGF19 may serve as a molecular anchor, linking tumor biology to imaging phenotypes. For instance, radiomic signatures from CT or MRI scans might be correlated with serum FGF19 dynamics to predict treatment response more accurately. Such integrative strategies align with the broader vision of precision oncology, where molecular and imaging data converge to guide both surveillance and therapeutic decisions [24].

Finally, the adoption of FGF19 into clinical practice will depend on addressing logistical and economic challenges. Standardized, cost-effective assays must be developed to ensure reproducibility and accessibility beyond specialized centers. Validation studies should also explore how FGF19 performs in real-world settings, including patients with coexisting metabolic liver disease, cholestasis, or other confounding conditions. Ultimately, the future of FGF19 as a biomarker in AFP-low HCC will depend on its ability to demonstrate added value over existing tools, to be incorporated into multi-parameter risk models, and to support personalized surveillance strategies after locoregional therapy [25].

Challenges and Limitations

Despite the promising potential of FGF19 as a biomarker in AFP-low hepatocellular carcinoma, several challenges hinder its current clinical application. One of the most important limitations is the lack of

standardization in FGF19 assays. Different laboratories employ varying platforms and cut-off values for serum FGF19 measurement, resulting in inconsistencies across studies. Without harmonized methods, it is difficult to establish clinically relevant thresholds that can reliably distinguish between treatment response, stable disease, and recurrence. Prospective studies are required to validate reproducible cut-offs and determine the optimal timing for FGF19 testing during follow-up after locoregional therapy [26].

Another limitation is the potential for confounding by non-malignant liver conditions. Because FGF19 plays a central role in bile acid regulation, its levels may be altered in patients with cholestasis, metabolic liver disease, or other hepatobiliary disorders. This raises the possibility of false positives in surveillance, particularly in cirrhotic patients who already have complex biochemical profiles. Moreover, FGF19 expression can be influenced by systemic metabolic conditions such as obesity and diabetes, which frequently coexist in patients with hepatocellular carcinoma. These overlapping influences complicate the interpretation of elevated FGF19 levels and necessitate further research to determine its specificity as a biomarker [27].

The current evidence base for FGF19 is also limited in scope. Most available studies are retrospective and involve relatively small cohorts, with heterogeneity in treatment modalities, disease stage, and background liver disease. Few studies have specifically examined AFP-low patients as a distinct subgroup, despite this being the population of greatest clinical need. Furthermore, data on serial FGF19 monitoring in large prospective cohorts are lacking. Without such validation, it remains uncertain whether FGF19 can be reliably incorporated into surveillance algorithms or used to guide clinical decision-making in everyday practice [28].

Practical and economic considerations must also be acknowledged. Advanced biomarker testing, including FGF19 assays, may not be widely accessible in resource-limited settings where hepatocellular carcinoma is most prevalent. MRI and CT already impose significant financial burdens on healthcare systems, and the addition of specialized biomarker testing could exacerbate inequalities in access to high-quality surveillance. Before FGF19 can be adopted into routine follow-up protocols, its cost-effectiveness relative to existing biomarkers and imaging strategies must be established. Only with standardized, affordable, and validated assays can FGF19 fulfill its potential as a clinically useful biomarker in AFP-low HCC [29].

Conclusion

The management of hepatocellular carcinoma remains particularly complex in patients with low or normal alpha-fetoprotein, as conventional biomarkers fail to provide meaningful guidance for post-treatment surveillance. In this context, fibroblast growth factor 19 has emerged as a promising candidate that reflects key biological mechanisms of hepatocarcinogenesis while offering measurable clinical correlations with treatment response and recurrence. Its ability to capture tumor activity in AFP-low patients following locoregional therapy addresses a critical unmet need, complementing radiological monitoring and enhancing early detection of disease relapse.

While the current body of evidence highlights the biological plausibility and clinical potential of FGF19, important gaps remain before it can be integrated into routine practice. Large-scale, prospective validation is required to standardize assays, establish thresholds, and confirm its prognostic accuracy in diverse patient populations. Integration of FGF19 into multimodal models that combine biomarkers with imaging holds promise for achieving more precise and individualized surveillance strategies. Ultimately, FGF19 may not

only serve as a biomarker but also as a therapeutic target, bridging the gap between molecular biology and clinical oncology. Its careful evaluation in AFP-low HCC could pave the way toward more effective follow-up protocols and improved outcomes in this challenging subgroup.

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