


Review

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# Importance of critical tumor features in multidisciplinary multi-parametric assessment of HCC

Quirino Lai<sup>1</sup> , Leonardo Centonze<sup>2,3</sup>, Matteo Renzulli<sup>4,5</sup>, Nicolò Brandi<sup>6,7</sup>, Bruno Sensi<sup>8</sup>, Tommaso Maria Manzia<sup>8</sup>, Daniele Nicolini<sup>9</sup>, Luca Viganò<sup>10,11</sup>, the Associazione Italiana per lo Studio del Fegato (AISF) HCC Special Interest Group

<sup>1</sup>General Surgery and Organ Transplantation Unit, Department of General and Specialty Surgery, Sapienza University of Rome, AOU Policlinico Umberto I, Rome 00161, Italy.

<sup>2</sup>Department of General Surgery and Transplantation, Niguarda Ca' Granda Hospital, Milan 20162, Italy.

<sup>3</sup>Clinical and Experimental Medicine PhD Program, Università degli Studi di Modena e Reggio Emilia, Modena 41121, Italy.

<sup>4</sup>Radiology Unit, Morgagni-Pierantoni Hospital, Forlì 47121, Italy.

<sup>5</sup>Department of Medical and Surgical Sciences, University of Bologna, Bologna 40126, Italy.

<sup>6</sup>Radiology Unit, Ospedale "degli Infermi", Faenza 48018, Italy.

<sup>7</sup>Department of Medical and Surgical Sciences, University of Bologna, Bologna 40126, Italy.

<sup>8</sup>HPB and Transplant Unit, Department of Surgical Science, The University of Rome Tor Vergata, Fondazione PTV, Rome 00133, Italy.

<sup>9</sup>S.O.D. Clinica di Chirurgia dei Trapianti, Azienda Ospedaliero-Universitaria "Ospedali Riuniti" di Ancona, Ancona 60126, Italy.

<sup>10</sup>Hepatobiliary Unit, Department of Minimally Invasive General and Oncologic Surgery, Humanitas Gavazzeni University Hospital, Bergamo 24125, Italy.

<sup>11</sup>Department of Biomedical Sciences, Humanitas University, Milan 20090, Italy.

**Correspondence to:** Dr. Quirino Lai, General Surgery and Organ Transplantation Unit, Department of General and Specialty Surgery, Sapienza University of Rome, AOU Policlinico Umberto I, Viale del Policlinico 155, Rome 00161, Italy. E-mail: lai.quirino@libero.it

**How to cite this article:** Lai Q, Centonze L, Renzulli M, Brandi N, Sensi B, Manzia TM, Nicolini D, Viganò L, Group the Associazione Italiana per lo Studio del Fegato (AISF) HCC Special Interest. Importance of critical tumor features in multidisciplinary multi-parametric assessment of HCC. *Hepatoma Res.* 2025;11:14. <https://dx.doi.org/10.20517/2394-5079.2024.146>

**Received:** 22 Dec 2024 **First Decision:** 18 Mar 2025 **Revised:** 22 Apr 2025 **Accepted:** 14 May 2025 **Published:** 5 Jun 2025

**Academic Editor:** Sudhakar K. Venkatesh **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

## Abstract

Hepatocellular carcinoma (HCC) is a complex malignancy that necessitates a multidisciplinary approach to optimize diagnosis, treatment, and management. The Barcelona Clinic Liver Cancer (BCLC) staging system remains a cornerstone for clinical decision making, yet its real-world application often requires a more personalized strategy. A multi-parametric framework integrating tumor morphology, biological markers, imaging characteristics,



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and inflammatory responses has gained traction in refining therapeutic selection. Key factors such as tumor location, size, and vascular involvement critically impact treatment feasibility and efficacy. Biomarkers like alpha-fetoprotein (AFP) provide prognostic value, while novel markers such as des-gamma-carboxy prothrombin (DCP) enhance risk stratification for curative therapies. Inflammation-based indices, including neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, contribute to recurrence and survival predictions. Advanced imaging modalities, such as positron emission tomography (PET), offer valuable insights into tumor biology and treatment response, guiding both surgical and non-surgical interventions. Despite its promise, implementing this multi-parametric, patient-tailored approach in clinical practice presents challenges, including variability in biomarker reliability, accessibility of advanced imaging, and the need for interdisciplinary coordination. Overcoming these limitations requires seamless collaboration among hepatologists, oncologists, radiologists, and surgeons to integrate diverse data streams into cohesive treatment algorithms. By leveraging individualized, data-driven strategies, this evolving paradigm aims to improve patient outcomes and advance precision medicine in HCC care.

**Keywords:** Hepatocellular carcinoma, barcelona clinic liver cancer, tumor markers, alpha-fetoprotein, des-gamma-carboxy prothrombin, inflammation-based indices, neutrophil-to-lymphocyte ratio, positron emission tomography

## INTRODUCTION

Hepatocellular carcinoma (HCC) remains a complex malignancy that requires a multifaceted approach for effective diagnosis, treatment, and prognosis<sup>[1]</sup>. Over the past quarter century, the decision-making process for HCC treatment has been guided by the Barcelona Clinic Liver Cancer (BCLC) staging classification, with minor adjustments implemented over time since its initial version<sup>[2,3]</sup>. The parameters composing the BCLC are correlated with the tumor stage (i.e., size, number, vascular invasion of the tumor, presence of extrahepatic spread), liver function (i.e., Child-Pugh Score), and ECOG performance status (PS)<sup>[2,3]</sup>.

However, the BCLC staging-based hierarchy has faced increasing criticism due to the gap between the therapies proposed for different stages and the real-world therapeutic approaches adopted<sup>[4]</sup>. Recently, a novel concept of multi-parametric therapeutic hierarchy has been proposed, establishing a hierarchy of HCC therapies beginning with curative strategies and moving to less effective options<sup>[5]</sup>.

The decision to consider a patient suitable for a specific therapy depends on multiple factors not commonly included in the BCLC staging system, such as patient fitness<sup>[6]</sup>, alternative parameters of liver function<sup>[7]</sup>, feasibility<sup>[8]</sup>, and critical tumor features.

Among these tumor features, several elements need to be assessed to guide clinical decisions, including tumor characteristics, biological markers, imaging findings, and inflammatory responses. Key aspects include the tumor's anatomical location, alpha-fetoprotein (AFP), additional tumor markers such as des-gamma-carboxy prothrombin (DCP)/protein induced by vitamin K absence (PIVKA), inflammatory markers, radiological tumor response assessments, and positron emission tomography (PET) scans. This comprehensive review explores in detail how these factors intersect to shape HCC treatment strategies and patient outcomes.

## TUMOR LOCATION

Tumor location can influence both the feasibility and effectiveness of curative-intent treatments (resection, ablation) for HCC. Despite its evident and intuitive clinical significance, the role of tumor location in HCC treatment allocation is limited by the diverse clinical scenarios that this crucial factor could impact [Figure 1].

## Tumor Location

### *Superficial tumor:*

- more accessible surgically,
- laparoscopically, robotically, open
- minor anatomic resections providing adequate tumor-free margin

### *Deep-located tumor:*

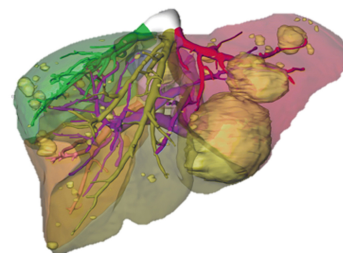
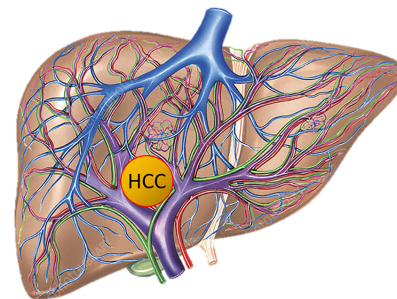
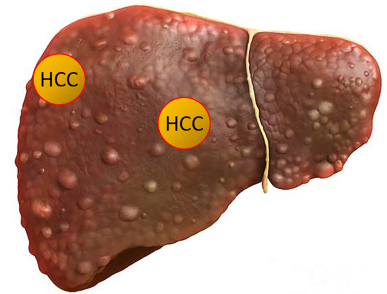
- technically resectable through major hepatectomies
- smaller FLRs contraindicate surgery

### *Perivascular tumor:*

- high risk of positive surgical margins, need for extended hepatectomies
- proximity to major vessels (>3 mm) can reduce effectiveness of LRT
- proximity to main portal vein branches may increase risk of vascular and biliary complications

### *Modern 3D reconstruction:*

- can aid in patient selection and preoperative surgical planning



**Figure 1.** Specific characteristics of tumor location in the decision of therapies to adopt. HCC: Hepatocellular carcinoma; LRT: locoregional therapies; FLR: future liver remnant.

According to modern multi-parametric treatment allocation in HCC settings<sup>[5]</sup>, PS, liver function (Child score, MELD), and tumor characteristics like nodule number, size, and location are essential drivers for curative treatment allocation. It is well established that multinodular tumors often benefit less from surgical approaches, making such cases relatively contraindicated for resection<sup>[9,10]</sup>. Tumor location can be broadly defined based on the position of the HCC nodule(s) within the liver parenchyma (superficial/deep) and its relationship to major vascular or biliary structures (perivascular).

Surgical resection remains the primary curative treatment option for HCC, along with liver transplantation (LT), given adequate PS (ECOG PS 0-1), underlying liver function (Child-Pugh A5-B7), and sufficient future liver remnant (FLR > 30%-40%)<sup>[11]</sup>. Superficial tumors are more accessible surgically, whether approached laparoscopically, robotically, or via open surgery, and are more likely to be treated with minor anatomic resections (segmentectomies; sub-segmentectomies), provided an adequate tumor-free margin can be achieved<sup>[12]</sup>. Deep-located tumors pose a clinical rather than technical challenge: while technically resectable through major hepatectomies (hemihepatectomy, trisectionectomy), smaller FLRs may contraindicate surgery in this setting. Similarly, perivascular tumors present challenges due to the high risk of positive surgical margins and the need for extended hepatectomies when the tumor is closely associated with major portal branches. Modern 3D reconstructions can aid in patient selection and preoperative surgical planning<sup>[13,14]</sup>. Emerging evidence supports using conversion therapies (e.g., locoregional treatments combined with systemic therapy)<sup>[15]</sup> and advanced surgical techniques like the Associating Liver Partitioning and portal vein Ligation for Staged hepatectomy (ALPPS)<sup>[16]</sup> to expand the role of curative surgery in these challenging scenarios. Like surgical resection, HCC ablation is significantly influenced by tumor location, which affects the choice of energy source [radiofrequency ablation (RFA), microwave, cryoablation] and technical approach (percutaneous *vs.* laparoscopic).

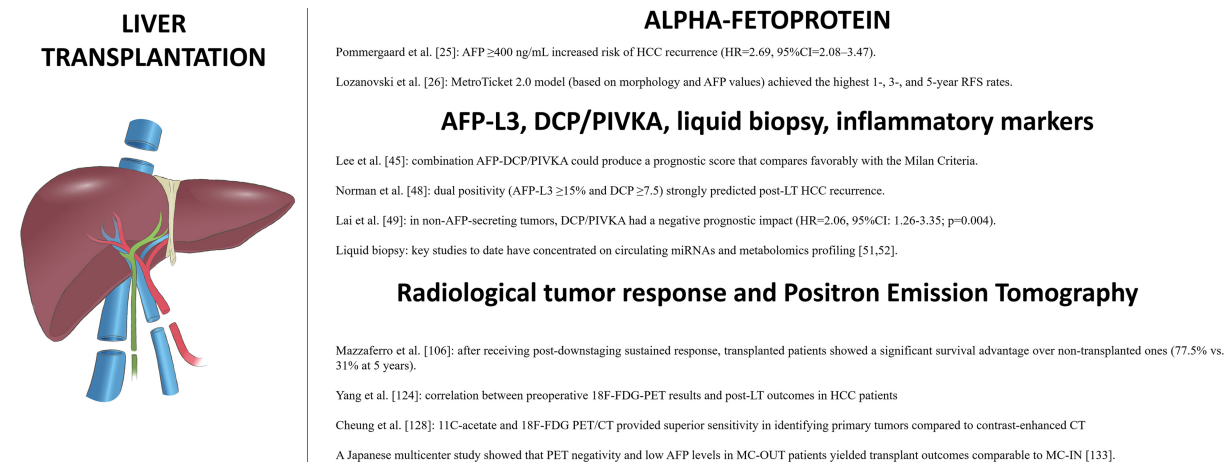
For perivascular lesions, it is well-documented that proximity to major vessels (> 3 mm) can reduce thermal ablation effectiveness due to the heat-sink effect<sup>[17]</sup>. In this regard, recent studies demonstrate that microwave rather than RFA yields better outcomes for local tumor control<sup>[18,19]</sup>. However, proximity to the main portal vein branches may increase the risk of vascular and biliary complications. Although its clinical role is still being evaluated, cryoablation appears promising for such cases<sup>[20]</sup>. Proximity to the liver surface may increase the risk of tumor seeding and organ injury (colon, gallbladder, heart), making laparoscopic ablation a highly effective treatment, particularly for smaller tumors<sup>[21,22]</sup>.

## AFP

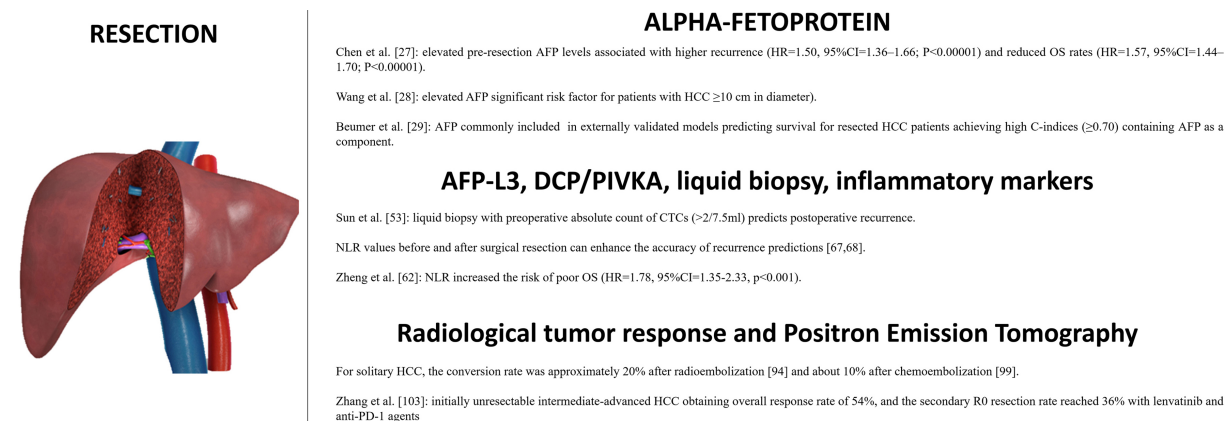
AFP is a key biomarker widely used in diagnosing and monitoring HCC<sup>[23]</sup>. The prognostic significance of AFP has been extensively explored across various therapies for HCC management, although this marker has not yet been universally incorporated into decision-making models for treatment [Figures 2, 3 and 4].

He *et al.* conducted a meta-analysis investigating AFP levels post-treatment across different therapies, including 4,726 HCC patients. Their analysis showed that post-treatment AFP response was significantly associated with overall survival (OS) [hazard ratio (HR) = 0.41, 95% confidence interval (CI) = 0.35-0.47,  $P < 0.001$ ], progression-free survival (PFS) (HR = 0.46, 95%CI = 0.39-0.54,  $P < 0.001$ ), and recurrence-free survival (RFS) (HR = 0.41, 95%CI = 0.29-0.56,  $P < 0.001$ )<sup>[24]</sup>. In a subgroup analysis focusing on OS, all therapies demonstrated a beneficial effect of AFP decline [curative therapies: HR = 0.52,  $P < 0.001$ ; locoregional therapies (LRT): HR = 0.40,  $P < 0.001$ ; systemic therapies: HR = 0.33,  $P < 0.001$ ; combined therapies: HR = 0.41,  $P = 0.02$ ]<sup>[24]</sup>.

Analyzing specific therapies for HCC treatment, AFP has been widely investigated in the context of LT. Pommergaard *et al.* demonstrated that AFP is a reliable biomarker for predicting post-LT recurrence, supporting its inclusion in post-transplant monitoring protocols<sup>[25]</sup>. Specifically, pooled data from 17 studies indicated an association between elevated pre-LT AFP ( $\geq 400$  ng/mL) and increased risk of HCC recurrence (HR = 2.69, 95%CI = 2.08-3.47)<sup>[25]</sup>. Lozanovski *et al.* highlighted the importance of combining AFP with tumor morphology to determine LT eligibility: in a network meta-analysis of 60,850 HCC transplant patients, those selected for LT using the MetroTicket 2.0 model - based on morphology and AFP values - achieved the highest 1-, 3-, and 5-year RFS rates, supporting the superiority of a combined biology-morphology approach for improved survival outcomes<sup>[26]</sup>.



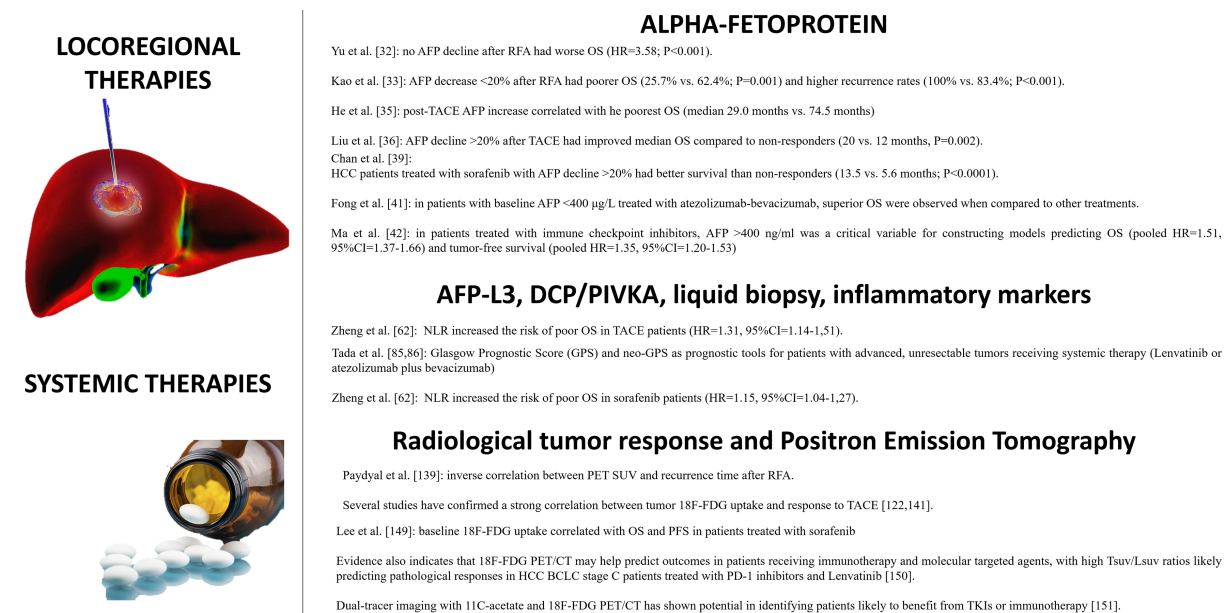
**Figure 2.** Articles focused on liver transplantation. AFP: Alpha-fetoprotein; AFP-L3: Lens culinaris agglutinin-reactive AFP; DCP: des-gamma-carboxy prothrombin; PIVKA: protein induced by vitamin K absence or antagonist; RFS: recurrence-free survival; LT: liver transplantation; HCC: hepatocellular carcinoma; PET: positron emission tomography; 18F-FDG: 18F-fluorodeoxyglucose; CT: computed tomography; MC-IN: within Milan Criteria; MC-OUT: beyond Milan Criteria; miRNA: microRNA.



**Figure 3.** Articles focused on liver resection. AFP: Alpha-fetoprotein; AFP-L3: Lens culinaris agglutinin-reactive fraction of AFP; DCP: des-gamma-carboxy prothrombin; PIVKA-II: protein induced by vitamin K absence or antagonist-II; CTC: circulating tumor cell; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; RFS: recurrence-free survival; PD-1: programmed cell death protein 1; R0: complete resection with negative margins.

For patients undergoing liver resection, AFP also serves as a crucial prognostic marker. In a meta-analysis (61 studies, 35,461 patients), Chen *et al.* found that elevated pre-resection AFP levels were associated with poor outcomes, including higher recurrence (HR = 1.50, 95%CI = 1.36-1.66,  $P < 0.00001$ ) and reduced OS rates (HR = 1.57, 95%CI = 1.44-1.70,  $P < 0.00001$ )<sup>[27]</sup>. Supporting these results, Wang *et al.* demonstrated in a meta-analysis (13 studies, 7,609 patients) that elevated AFP was a significant risk factor for patients undergoing hepatectomy for large HCC tumors ( $\geq 10$  cm in diameter), correlating with increased recurrence and mortality<sup>[28]</sup>. Beumer *et al.* reviewed all externally validated models predicting survival for resected HCC patients, finding that AFP has commonly been included in these models since 2007, with five of the six models achieving high C-indices ( $\geq 0.70$ ) containing AFP as a component<sup>[29]</sup>. Additionally, several nomograms incorporating AFP have demonstrated strong predictive performance for individual prognosis in resected patients<sup>[30,31]</sup>.





**Figure 4.** Articles focused on locoregional treatments and systemic therapies. AFP: Alpha-fetoprotein; AFP-L3: Lens culinaris agglutinin-reactive fraction of AFP; DCP: des-gamma-carboxy prothrombin; PIVKA-II: protein induced by vitamin K absence or antagonist-II; RFA: radiofrequency ablation; TACE: transarterial chemoembolization; OS: overall survival; PFS: progression-free survival; NLR: neutrophil-to-lymphocyte ratio; GPS: Glasgow Prognostic Score; neo-GPS: neo-Glasgow Prognostic Score; PET: positron emission tomography; SUV: standardized uptake value; 18F-FDG: fluorine-18 fluorodeoxyglucose; 11C-acetate: carbon-11 acetate; CT: computed tomography; TSUV: tumor standardized uptake value; IAUU: intrahepatic arterial uptake value; PD-1: programmed cell death protein 1; TKI: tyrosine kinase inhibitor; HCC: hepatocellular carcinoma.

Regarding RFA, Yu *et al.* reported that patients without AFP decline after the procedure had higher rates of radiologic progression (71.4% vs. 54.8%), faster HCC progression post-RFA (HR = 1.90,  $P < 0.001$ ), and worse OS (HR = 3.58,  $P < 0.001$ )<sup>[32]</sup>. Kao *et al.* ( $N = 313$ ) confirmed these findings, showing that AFP non-responders (AFP decrease  $< 20\%$  after RFA) had poorer OS (25.7% vs. 62.4%,  $P = 0.001$ ) and higher recurrence rates (100% vs. 83.4%,  $P < 0.001$ )<sup>[33]</sup>. Jiang *et al.* evaluated the combined use of RFA and transarterial chemoembolization (TACE), reporting that, one and two weeks post-treatment, the number of complete and partial responders was higher in patients receiving the combined approach, with a corresponding significant AFP reduction<sup>[34]</sup>.

In studies focused on TACE, a Chinese study of 177 HCC patients with post-TACE recurrence showed that patients with post-TACE AFP increases had the poorest OS (median 29.0 months vs. 74.5 months in those with AFP decline and 64.0 months in patients with stable AFP levels). Multivariable analysis confirmed AFP change after TACE as a significant independent OS risk factor<sup>[35]</sup>. Another Chinese study ( $N = 376$ ) on BCLC B patients found that cases with an AFP response (decline  $> 20\%$ ) after TACE had improved median OS compared to non-responders (20 months vs. 12 months,  $P = 0.002$ ). AFP response also significantly correlated with imaging response ( $P < 0.001$ ), and the Cox proportional hazards model identified AFP response as an independent OS factor (HR = 0.59, 95%CI = 0.45-0.78,  $P < 0.001$ )<sup>[36]</sup>.

In a European multicenter study ( $N = 422$ ) covering all LRT, the combination of radiological response and AFP decline (AFP slope  $< 15$  ng/mL/month) post-LRT identified a subgroup of LT candidates with low risk of post-LT recurrence, regardless of Milan Criteria tumor status<sup>[37]</sup>.

In a meta-analysis on TACE combined with lenvatinib, a multi-receptor tyrosine kinase inhibitor (TKI), patients receiving the combination showed a significant reduction in AFP levels (standard mean difference = 1.22, 95%CI = 0.67-1.78,  $P < 0.0001$ ) compared to patients receiving TACE or lenvatinib alone<sup>[38]</sup>.

Systemic therapies have also been linked with AFP outcomes. A study from Hong Kong ( $N = 188$ ) demonstrated that HCC patients treated with the TKI sorafenib, with an AFP decline ( $> 20\%$ ), experienced better survival than non-responders (13.5 months vs. 5.6 months,  $P < 0.0001$ ). Multivariable analysis confirmed AFP response as significantly associated with survival (HR = 0.41, 95%CI = 0.27-0.63,  $P < 0.0001$ )<sup>[39]</sup>. An international study ( $N = 827$ ) similarly found that sorafenib-treated patients with initially high AFP had poorer OS and tumor-free survival rates<sup>[40]</sup>.

In a recent network meta-analysis exploring different therapies, it was observed that in patients with baseline AFP  $< 400 \mu\text{g/L}$ , the combination of atezolizumab-bevacizumab yielded superior OS compared to other treatments. However, in patients with baseline AFP  $\geq 400 \mu\text{g/L}$ , tremelimumab-durvalumab ranked first, followed by atezolizumab-bevacizumab and nivolumab, suggesting that initial AFP values could guide first-line therapy choices<sup>[41]</sup>.

Lastly, a meta-analysis on 47 studies ( $N = 7,649$ ) involving HCC patients treated with immune checkpoint inhibitors identified AFP  $> 400 \text{ ng/mL}$  as a critical variable for constructing models predicting OS (pooled HR = 1.51, 95%CI = 1.37-1.66) and tumor-free survival (pooled HR = 1.35, 95%CI = 1.20-1.53)<sup>[42]</sup>.

Apart from the potential benefit correlated with the integration of AFP into the decision-making models, some limitations of this biomarker must be reported. It is well known that AFP lacks sufficient sensitivity and specificity for HCC detection, particularly in early-stage disease, with a significant proportion of HCC patients having normal AFP levels or elevated AFP values in patients with chronic liver diseases without any presence of HCC<sup>[43]</sup>. However, the same limitations also exist in the setting of prognosis. While elevated AFP levels correlate with tumor burden and aggressive tumor behavior, cut-off values for prognostication vary across studies, leading to inconsistencies in clinical application<sup>[24-27]</sup>. Post-treatment AFP dynamics are also useful prognostic indicators, but the threshold for defining an AFP response is not standardized, affecting comparability across studies<sup>[37]</sup>. Lastly, AFP performance varies significantly based on patient demographics and geographical regions. Asian populations, where HBV-related HCC is predominant, tend to exhibit higher AFP levels than Western populations, where HCC is often linked to HCV or steatohepatitis<sup>[44]</sup>. All of these aspects should be considered when AFP is considered in terms of the decision-making process.

## NEW TUMOR MARKERS

One factor that significantly influences prognosis is the intrinsic biology (aggressiveness) of HCC. Accordingly, biological features of the tumor could ideally be used to predict outcomes and guide therapeutic decisions. However, most well-studied features can only be revealed through histological examination (which is not routinely performed preoperatively in HCC), while blood-based biomarkers have been less thoroughly investigated. Recently, there has been a surge in studies focusing on biomarkers predictive of prognosis or response to certain treatments, though none have yet achieved widespread validation. The coming years promise to shift these experimental findings into everyday clinical practice. As of 2024, investigated biomarkers include AFP-L3, DCP/PIVKA, and liquid biopsy [Figures 2, 3 and 4].

Several markers have been employed to predict post-LT or post-resection survival. Lee *et al.* were among the first to demonstrate how the combination of AFP and DCP/PIVKA could produce a prognostic score that compares favorably with the Milan Criteria<sup>[45]</sup>. A subsequent meta-analysis confirmed the utility of DCP/PIVKA in predicting recurrence following LT<sup>[46]</sup>.

A study from Japan examined a population of resected cases, where AFP-L3 was associated with progression from moderately to poorly differentiated HCC, whereas DCP/PIVKA showed greater specificity for vascular invasion<sup>[47]</sup>. However, most studies on these alternative tumor markers primarily originated from Eastern cohorts.

Only recently have some Western studies been published. A study from the US showed that dual positivity for AFP-L3  $\geq 15\%$  and DCP  $\geq 7.5$  strongly predicted post-LT HCC recurrence, further refining LT selection criteria and identifying high-risk patients who require additional locoregional therapy before LT<sup>[48]</sup>.

A multicenter study based on European and Japanese cases found that in patients with non-AFP-secreting tumors, DCP/PIVKA had a negative prognostic impact (HR = 2.06, 95%CI: 1.26-3.35,  $P = 0.004$ ). When categorizing the entire population into four groups based on AFP levels ( $\leq$  or  $> 20$  ng/mL) and DCP/PIVKA ( $\leq$  or  $> 300$  mUA/mL) at the time of LT, the lowest recurrence rates were observed in the low AFP-DCP/PIVKA group (5-year recurrence rate = 8.0%). Conversely, the high AFP-DCP/PIVKA group had the poorest outcome (5-year recurrence rate = 35.1%)<sup>[49]</sup>. While elevated DCP/PIVKA and AFP-L3 levels correlate with tumor burden, vascular invasion, and aggressive tumor behavior, different cut-off values have been proposed across studies, leading to inconsistencies in clinical application<sup>[45-49]</sup>. No studies exploring the dynamics of these markers in the prognostic setting have been published. Further studies are necessary to expand the use of these markers in routine clinical practice<sup>[50]</sup>.

Various prognostic biomarkers, including DNA mutations, gene expression (gene signatures), DNA methylation, and miRNAs, have been studied extensively, but the primary limitation is the need for tissue biopsy. For this reason, liquid biopsy has gained considerable interest in HCC. This approach involves analyzing circulating tumor cells (CTCs), DNA, or microparticles found in blood. In the LT setting, key studies to date have concentrated on circulating miRNAs and metabolomics profiling<sup>[51,52]</sup>.

In the context of liver resection, liquid biopsy has been more extensively investigated. CTCs have been the focus of much study by Chinese researchers, who report that both the preoperative absolute ( $> 2$  CTCs/7.5 mL) or relative ( $> 0.01\%$ ) count predict postoperative recurrence<sup>[53,54]</sup>. Likewise, their presence or increase after resection (quite intuitively) signals the development of metastases<sup>[55]</sup>. The CTC subtype also appears to be significant, with the presence or proportion of mesenchymal CTCs correlating with early recurrence, intrahepatic and lung metastases, and decreased survival<sup>[56,57]</sup>. In 2017, Xu *et al.* found that circulating tumor DNA methylation markers are strongly correlated with prognosis and survival. However, the cost of these analyses has hindered their widespread adoption<sup>[58]</sup>. Circulating miRNAs have also been implicated in recurrence prediction after resection, with circAKT3 being associated with early recurrence and reduced OS<sup>[59]</sup>.

Despite promising findings, several limitations challenge the clinical implementation of liquid biopsy in the context of liver resection. First, there is a lack of standardization in the methodologies used to detect and quantify CTCs, with varying definitions of absolute and relative thresholds, and inconsistencies in identifying specific subtypes such as mesenchymal CTCs. These variations can lead to divergent results and complicate the reproducibility of findings across different centers. Additionally, while circulating tumor



DNA methylation markers and circulating miRNAs show strong correlations with prognosis and recurrence, the high costs associated with these advanced analyses have hindered their widespread adoption. Technical complexities in processing and interpreting these molecular assays further limit their routine use in clinical practice. Overall, these challenges underscore the need for further standardization, cost reduction, and validation in diverse patient populations before liquid biopsy can be reliably integrated into HCC management following liver resection.

## INFLAMMATION-BASED MARKERS

The well-established etiological link between chronic inflammation and carcinogenesis has led researchers to explore novel prognostic markers tied to the inflammatory status of HCC patients<sup>[60]</sup>. Among these, the prognostic value of two lymphocyte-based scores - the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) - has been widely studied across various stages of HCC<sup>[61-64]</sup> [Figures 2, 3 and 4]. A recent Eastern meta-analysis of sixteen studies including 4,654 patients demonstrated that a high baseline NLR significantly correlates with poor prognosis or HCC recurrence. The pooled area under the curve (AUC) of the summary receiver operating characteristic (SROC), representing prognostic accuracy, was 0.75 (95%CI: 0.71-0.78), while the pooled diagnostic odds ratio (DOR) was 6.347 (95%CI: 5.450-7.391)<sup>[65]</sup>. Additional studies<sup>[66]</sup>, including a large meta-analysis of 6,318 patients, confirmed that elevated NLR and PLR levels before HCC treatment are linked to lower OS and earlier recurrence. Notably, subgroup analyses indicated that the prognostic reliability of NLR and PLR holds across different treatment modalities, including curative approaches (e.g., LT and hepatic resection) and palliative treatments (e.g., TACE, sorafenib, and RFA)<sup>[62]</sup>. Furthermore, monitoring dynamic changes in NLR values before and after treatment - especially in patients undergoing surgical resection - can enhance the accuracy of recurrence predictions, supporting the development of patient-specific surveillance protocols and therapeutic strategies<sup>[67,68]</sup>. The association of high preoperative NLR with histological features, such as microvascular invasion (MVI), multifocality, and large (> 5 cm) tumor size, serves as another indicator of biological aggressiveness with valuable clinical implications<sup>[66]</sup>. Given the expanding evidence linking NLR<sup>[69-72]</sup> and PLR<sup>[73-75]</sup> to recurrence and survival in the setting of LT, several authors have integrated these inflammatory markers into prominent scoring systems for HCC patients awaiting LT, such as the MORAL and TRAIN scores, thereby validating their use as selection tools for transplant candidates<sup>[76,77]</sup>.

In addition to neutrophils and platelets, monocytes have emerged as significant regulators of tumor progression<sup>[78]</sup>. A reduction in circulating monocyte levels may signal their recruitment to the tumor microenvironment, where they differentiate into tumor-associated macrophages (TAMs), ultimately suppressing T-cell function and fostering tumor growth and angiogenesis<sup>[79]</sup>. A meta-analysis of 7 studies comprising 2,738 surgically treated patients showed that an increased lymphocyte-to-monocyte ratio (LMR) (greater than 3) was predictive of poor overall and disease-free survival<sup>[80]</sup>.

The Glasgow Prognostic Score (GPS), which combines C-reactive protein (CRP) and albumin values, is one of the earliest and most widely utilized inflammation-based scoring systems<sup>[81]</sup>. Three Japanese studies validated the use of GPS in the preoperative setting for predicting overall and disease-free survival in HCC patients undergoing liver resection<sup>[82-84]</sup>. Recently, two multicenter studies by Tada *et al.* confirmed GPS and neo-GPS (using ALBI grade instead of serum albumin) as prognostic tools for patients with advanced, unresectable tumors receiving systemic therapy (Lenvatinib or atezolizumab plus bevacizumab)<sup>[85,86]</sup>.

It is worth noting that several factors can potentially impede the clinical application of inflammation-based scores. First, the optimal cut-off value for these indexes is not well defined, as different studies have explored varying clinical settings; NLR cut-off values range widely from 1.5 to 5<sup>[65,66]</sup>, although for patients

undergoing curative treatment, the most reliable predictive values determined by ROC analysis are  $\geq 2.81$ <sup>[87,88]</sup> or  $\geq 5$ <sup>[77,89]</sup>. Similar uncertainty applies to PLR (ranging from 75.3 to 167.7) and GPS, where the most prognostically informative cut-off values appear to be  $\geq 150$  and  $\geq 1$ , respectively<sup>[81,90]</sup>. Second, most studies in these meta-analyses were conducted in Asian institutions, necessitating caution in applying these findings to Western populations. Finally, inflammatory serum biomarkers can be affected by various conditions, such as acute infections, hematologic disorders, hypersplenism, gastrointestinal bleeding, and systemic inflammatory diseases - common challenges in patients with end-stage liver disease.

In the complex landscape of HCC management, the independent prognostic role of inflammation-based indexes remains to be conclusively confirmed. Nonetheless, their cost-effectiveness and accessibility support their inclusion in clinical practice. The existing evidence indicates that, when incorporated into a multi-parametric algorithm alongside other validated biological, clinical, and radiological factors, inflammation-based markers can improve risk stratification and inform therapeutic decisions in HCC patients.

## RADIOLOGICAL TUMOR RESPONSE

In modern oncology, the radiological response to systemic or LRT serves as a surrogate marker for tumor biology, with responders showing a better prognosis<sup>[91]</sup>. In HCC patients, the lack of reliable genetic biomarkers has rendered tumor response a key driver in precision medicine approaches [Figures 2, 3 and 4].

The preferred imaging modalities include multiphasic contrast-enhanced computed tomography (CT), which is considered the standard imaging technique for assessing HCC response, providing detailed arterial and venous phase enhancement patterns<sup>[91]</sup>. Multiphasic contrast-enhanced MRI with hepatobiliary agents also represents a relevant tool for detecting the radiological response, using the diffusion-weighted imaging and the hepatobiliary-specific contrast agents.

HCC patients demonstrate high response rates to various treatments: between 15% and 50% for TACE/embolization<sup>[92]</sup>, 40% and 80% for radioembolization<sup>[93,94]</sup>, and up to 35% for systemic therapies (combining atezolizumab and bevacizumab)<sup>[95]</sup>. In each case, responders have better survival outcomes than non-responders<sup>[92,94,96,97]</sup>. However, no study has yet shown a survival benefit from neoadjuvant therapy (chemoembolization or systemic therapy) prior to surgery.

The importance of radiological response has increased for its role in downsizing and downstaging disease, allowing unresectable patients to become resectable and making patients who initially did not meet transplant criteria eligible for transplantation.

For liver resection, conversion therapy is not standardized, resulting in varied conversion rates depending on study design, population, and administered treatment. In an unselected patient cohort receiving sorafenib or lenvatinib, the secondary resectability rate was less than 1%<sup>[98]</sup>, while in advanced HCC (i.e., unresectable or non-optimally resectable patients) treated with lenvatinib, it exceeded 5%<sup>[99]</sup>, and in intermediate-stage HCC treated with atezolizumab plus bevacizumab, it was over 5%<sup>[100]</sup>. For solitary HCC, the conversion rate was approximately 20% after radioembolization<sup>[94]</sup> and about 10% after chemoembolization<sup>[99]</sup>. Two randomized trials reported high secondary resectability rates in patients treated with oxaliplatin-based intra-arterial chemotherapy (11% and 24%)<sup>[101,102]</sup>. In a study by Zhang *et al.* involving 56 patients with unresectable intermediate-advanced HCC, the overall response rate was 54%, and the secondary R0 resection rate reached 36% with lenvatinib and anti-PD-1 agents<sup>[103]</sup>. Despite the diversity in approaches, all studies indicated adequate survival outcomes in resected patients, showing a clear benefit over non-resected patients.

For LT, radiologic tumor response serves as a foundation for expanding indications. Incorporating tumor response into the Metroticket 2.0 framework has optimized post-transplant prognosis estimation<sup>[104]</sup>. Moving from morphology to biology, the transplant community now accepts that HCC patients outside standard transplant criteria and without macrovascular invasion can be considered for transplantation if they have been effectively downstaged through treatments that yield a significant and sustained radiologic response<sup>[105]</sup>. Downstaging protocol success rates range from 30% to 90%, depending on criteria and strategies, and patients transplanted post-downstaging experience a survival benefit<sup>[106-109]</sup>. In a prospective analysis, Mazzaferro *et al.* achieved effective downstaging in 54 of 74 patients (73%, with 24 partial and 30 complete responders)<sup>[106]</sup>. Of these, 45 patients with sustained response were randomly assigned to transplantation or non-transplantation, with transplanted patients showing a significant survival advantage over non-transplanted ones (77.5% vs. 31% at 5 years). Mehta *et al.* analyzed 209 consecutive HCC patients undergoing downstaging per UNOS-DS criteria, finding that 174 (83%) met Milan criteria post-conversion, achieving a three-year post-transplant survival rate of 83%<sup>[107]</sup>. These encouraging findings have led to exploring downstaging protocols for patients with macrovascular invasion. In a multicenter study of 30 patients, Assalino *et al.* reported a five-year post-transplant survival rate of 60%<sup>[110]</sup>, potentially warranting guideline revisions. Modern systemic therapies may further expand eligibility, given their high response rates and theoretical effects on micrometastases<sup>[95]</sup>. However, only preliminary data are available<sup>[111,112]</sup>, and additional evaluations are needed, particularly for safety<sup>[113]</sup>.

Finally, two cautionary notes on radiological tumor response in HCC are noteworthy. First, assessments should follow modified RECIST criteria, which address limitations of standard RECIST criteria, such as evaluating viable cells in the absence of tumor shrinkage, cirrhosis-related pseudo-nodules, and enlarged non-tumoral lymph nodes<sup>[114]</sup>. Second, discrepancies can occur between radiologic and pathologic assessments, with the latter being the true prognostic determinant. Further advancements in predictive models incorporating new technologies such as machine learning and radiomics are warranted<sup>[115,116]</sup>.

## PET

PET using 18F-fluorodeoxyglucose (18F-FDG) is a well-established, noninvasive diagnostic tool widely employed for detecting various malignancies. However, its utility in diagnosing and staging HCC is limited, and current international guidelines do not recommend its routine use<sup>[117,118]</sup> [Figures 2, 3 and 4]. PET has shown value in identifying distant metastases, particularly in lymph nodes and bones<sup>[119]</sup>, differentiating between benign and malignant portal vein thrombi<sup>[120]</sup>, and predicting HCC recurrence post-treatment<sup>[119]</sup>. Specifically, F18-FDG PET can be a valuable imaging tool for patients with elevated AFP levels after HCC treatment or LT, especially when conventional imaging shows no abnormalities<sup>[121]</sup>. A meta-analysis<sup>[122]</sup> demonstrated that both a high Tumor standardized uptake value (SUV)/Liver SUV (Tsuv/Lsuv) ratio and elevated Tumor SUV values are significantly correlated with decreased survival rates. Recently introduced PET tracers targeting lipid metabolism, such as 11-C Acetate, have shown promising results, as their effectiveness seems to vary with tumor differentiation<sup>[123]</sup>.

Recent research has increasingly focused on the predictive value of FDG-PET in LT for HCC management. In 2006, Yang *et al.* first established a correlation between preoperative 18F-FDG-PET results and postoperative outcomes in HCC patients undergoing LT<sup>[124]</sup>. Subsequent studies have confirmed that PET positivity, SUVmax, and particularly the Tsuv/Lsuv ratio, are strong predictors of OS and RFS in HCC transplant recipients<sup>[122,125,126]</sup>. The robust prognostic impact of 18F-FDG-PET in LT can be attributed to its ability to detect poor tumor differentiation and MVI, which are critical indicators of HCC recurrence<sup>[125,127]</sup>.

New radiotracers like  $^{11}\text{C}$ -acetate have enhanced PET imaging sensitivity and specificity, with promising applications in LT. Cheung *et al.* reported that  $^{11}\text{C}$ -acetate and  $^{18}\text{F}$ -FDG PET/CT provided superior sensitivity in identifying primary tumors compared to contrast-enhanced CT<sup>[128]</sup>. Additionally, FDG PET has emerged as a stronger predictor of recurrence than the Milan Criteria in LT settings<sup>[129,130]</sup>. Building on this, several expanded HCC selection criteria incorporating FDG PET have been proposed. For instance, Hsu *et al.* developed a classification based on  $^{18}\text{F}$ -FDG uptake and UCSF criteria, categorizing patients into low-, intermediate-, and high-risk groups<sup>[131]</sup>. Hong *et al.* similarly recommended combining FDG PET with AFP levels to improve risk stratification, enhancing objectivity in selecting candidates for adult-to-adult living-donor LT<sup>[132]</sup>. A Japanese multicenter study validated this approach, showing that PET negativity and low AFP levels in patients beyond Milan criteria yielded transplant outcomes comparable to those within the criteria<sup>[133]</sup>. The National Cancer Center Korea (NCCCK) criteria further illustrate the role of PET in expanding transplant eligibility without affecting tumor-specific outcomes, outperforming the Milan criteria in predicting explant pathology (95% vs. 79% accuracy)<sup>[134]</sup>.

Numerous studies, despite challenges with small cohort sizes and heterogeneity, highlight the utility of  $^{18}\text{F}$ -FDG PET in predicting post-hepatectomy outcomes. Increased  $^{18}\text{F}$ -FDG uptake has emerged as a significant predictor of early recurrence and adverse histopathological features, including poor differentiation and MVI<sup>[135]</sup>. Post-surgical outcomes have been correlated with parameters such as Tsuv/Lsuv ratio<sup>[136]</sup>, metabolic tumor volume (MTV)<sup>[137]</sup>, and total lesion glycolysis (TLG)<sup>[138]</sup>.

For ablation therapies, PET's prognostic value has been derived from heterogeneous studies analyzing various treatments collectively. Paudyal *et al.* observed an inverse correlation between SUV and recurrence time after RFA, suggesting that higher SUV values might predict earlier HCC recurrence. Additionally, poorly and moderately differentiated HCCs showed higher  $^{18}\text{F}$ -FDG uptake compared to well-differentiated HCCs, with PET outperforming CT in early recurrence detection (92% vs. 75%)<sup>[139]</sup>. Ida *et al.* further indicated that PET-positive small HCCs post-RFA were associated with higher early metastatic recurrence risk and poorer survival, implying that RFA might not be the optimal treatment for  $^{18}\text{F}$ -FDG PET-positive HCCs<sup>[140]</sup>.

Regarding TACE, several studies have confirmed a strong correlation between tumor  $^{18}\text{F}$ -FDG uptake and response to LRT<sup>[122,141]</sup>. Given that TACE alone may not halt progression in HCC with high SUV ratios, some researchers advocate for early addition of other treatment modalities<sup>[142]</sup>. Newer studies have explored novel radiotracers in PET imaging, such as combining  $^{11}\text{C}$ -acetate PET and  $^{18}\text{F}$ -FDG PET to assess HCC response to TACE with or without bevacizumab, providing prognostic insights and guiding molecular therapy candidate selection<sup>[143]</sup>.

Limited data exist on  $^{18}\text{F}$ -FDG PET/CT utility in treatment planning for HCC patients undergoing 90Y-TARE, with small sample sizes producing mixed results. Hwang *et al.* reported that TLG - reflecting both  $^{18}\text{F}$ -FDG uptake and metabolically active tumor volume - was a superior OS predictor in 90Y-TARE-treated HCC patients compared to tumor dose delivered<sup>[144]</sup>. Conflicting findings among studies emphasize the need for further research to clarify  $^{18}\text{F}$ -FDG PET/CT's prognostic role in improving patient selection and outcome prediction for radioembolization<sup>[145,146]</sup>. Early dual-tracer PET/CT data with  $^{18}\text{F}$ -FDG and newer radiotracers like  $^{11}\text{C}$ -acetate and  $^{18}\text{F}$ -FCH show promise in 90Y-TARE contexts<sup>[147]</sup>.

PET imaging also shows potential in assessing systemic therapy outcomes for advanced HCC. Several studies have highlighted  $^{18}\text{F}$ -FDG PET/CT's prognostic value for OS and PFS in patients undergoing systemic therapy<sup>[148]</sup>. Lee *et al.* found that baseline  $^{18}\text{F}$ -FDG uptake correlated with OS and PFS in patients

treated with sorafenib, suggesting it could predict treatment outcomes in advanced HCC<sup>[149]</sup>.

Evidence also indicates that 18F-FDG PET/CT may help predict outcomes in patients receiving immunotherapy and molecular targeted agents, with high Tsuv/Lsuv ratios likely predicting pathological responses in HCC BCLC stage C patients treated with PD-1 inhibitors and Lenvatinib<sup>[150]</sup>. Dual-tracer imaging with 11C-acetate and 18F-FDG PET/CT has shown potential in identifying patients likely to benefit from TKIs or immunotherapy<sup>[151]</sup>.

18F-FDG PET can also aid in treatment decisions between systemic and LRT. For example, Lee *et al.* reported that in patients with high Tsuv/Lsuv ratios, concurrent intra-arterial chemotherapy with external-beam radiotherapy (CCRT) led to significantly better PFS and OS compared to TACE, even when adjusted for tumor size and number. Conversely, PFS and OS were not significantly different in patients treated with TACE or CCRT when Tsuv/Lsuv ratios were low<sup>[149]</sup>.

Finally, 18F-FDG PET/CT offers potential as a tool for evaluating treatment response, providing valuable insights for individualized therapy planning. A study reported that 18F-FDG uptake in HCC might predict rapid response to Lenvatinib<sup>[150]</sup>. The same group subsequently compared 18F-FDG PET/CT with other assessment tools (mRECIST, RECIST 1.1, and AFP) for evaluating lenvatinib response, suggesting Tsuv/Lsuv as a surrogate marker for treatment response. Additionally, 18F-FDG PET/CT provided detailed tumor localization, facilitating liver resection as part of conversion therapy in some cases<sup>[151]</sup>.

Despite these promising findings, further well-designed, large-scale prospective studies are needed to clarify PET's clinical significance in advanced HCC.

## CONCLUSION

Managing HCC effectively hinges on a detailed understanding of multiple diagnostic and prognostic factors. The tumor's location significantly affects the success of curative-intent therapies, while biomarkers like AFP and emerging tumor markers offer valuable prognostic data to refine patient selection and monitoring. Inflammatory indices complement this approach by indicating systemic responses, and imaging modalities - ranging from conventional radiological evaluations to PET scans - enhance precision in treatment planning and recurrence detection.

However, integrating these diverse factors poses challenges in resource-limited settings. Limited access to advanced diagnostic tools, variability in biomarker standardization, and the need for coordinated multidisciplinary teams may complicate the practical implementation of this comprehensive approach. The increased complexity and potential financial burden also raise concerns regarding the feasibility of widespread adoption.

Looking ahead, emerging technologies such as artificial intelligence-driven diagnostic algorithms, liquid biopsy platforms, and next-generation imaging techniques offer promising avenues to further refine HCC management. These innovations could improve early detection, optimize risk stratification, and guide more personalized therapeutic interventions, potentially bridging the gap between high-resource and resource-constrained environments. Ultimately, the success of this multi-parametric, multidisciplinary strategy will depend on continued collaboration among clinicians, researchers, and policymakers to address existing limitations and integrate these advances into routine clinical practice.



## DECLARATIONS

### Acknowledgments

The Authors thank the Associazione Italiana per lo Studio del Fegato (A.I.S.F.). Members of the Associazione Italiana per lo Studio del Fegato (AISF) HCC Special Interest Group: ASST Papa Giovanni XXIII Bergamo, Italy: Mauro Viganò; Campus Bio-Medico University Rome, Italy: Giovanni Galati; Cardarelli Hospital Naples, Italy: Marco Guarracino, Raffaella Tortora; Faenza Hospital, Italy: Nicolò Brandi; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Italy: Nicoletta De Matthaeis, Simone Famularo, Felice Giuliente, Giovanni B. Levi Sandri, Luca Miele, Francesca R. Ponziani; Foggia University Hospital, Italy: Rodolfo Sacco; Hospital of Faenza, Italy: Francesco G. Foschi; Humanitas University Milan, Italy: Luca Viganò; Imperial College London, UK: David J. Pinato; IS.ME.T.T. Palermo, Italy: Salvatore Gruttadauria, Duilio Pagano; Istituto Tumori Milano, Italy: Sherrie Bhooori, Carlo Sposito; National Institute of Gastroenterology Saverio de Bellis Bari, Italy: Raffaele Cozzolongo; Niguarda Ca' Granda Hospital Milan, Italy: Leonardo Centonze, Chiara Mazzearelli; Polytechnic University of Marche: Daniele Nicolini; University of Rome, Italy: Quirino Lai, Fabio Melandro; University Hospital of Verona, Italy: Paola Violi; University of Bari, Italy: Maria Rendina, Francesco D'Amico; University of Bologna, Italy: Matteo Cescon, Fabio Piscaglia, Matteo Renzulli, Francesco Tovoli, Franco Trevisani; University of Genoa, Italy: Edoardo G. Giannini, Giulia Pieri, Maria Corina Platz Torres; University of Milan, Italy: Massimo Iavarone, Angelo Sangiovanni; University of Milano Bicocca, Italy: Fabrizio Romano; University of Modena and Reggio Emilia, Italy: Stefano Di Sandro; University of Naples Federico II, Italy: Maria Guarino, Filomena Morisco; University of Padua, Italy: Giuseppina Brancaccio, Patrizia Burra, Umberto Cillo, Fabio Farinati, Michele Finotti, Martina Gambato, Filippo Pelizzaro, Francesco P. Russo, Alessandro Vitale; University of Palermo, Italy: Giuseppe Cabibbo, Ciro Celsa; University of Pisa, Italy: Paola Carrai, Laura Crocetti, Davide Ghinolfi; University of Salerno, Italy: Mario Masarone, Marcello Persico; University of Tor Vergata Rome, Italy: Ilaria Lenci, Tommaso M. Manzia, Bruno Sensi; University of Udine, Italy: Umberto Baccarani, Riccardo Pravisani; Vita-Salute San Raffaele University Milan, Italy: Andrea Casadei Gardini.

### Authors' contributions

Responsible for the conception, design, analysis, and writing of the study: Lai Q

Involved with the collection and interpretation of data: Lai Q, Centonze L, Renzulli M, Brandi N, Sensi B, Manzia TM, Nicolini D, Viganò L

Participated in data management, review and editing of the manuscript: Lai Q, Centonze L, Renzulli M, Brandi N, Sensi B, Manzia TM, Nicolini D, Viganò L

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

Not applicable.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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