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Direktor des Instituts: Univ.-Prof. Dr. med. Gerald Antoch

Prognostic Value of Early CT Morphologic Response
after DEB-TACE in Patients with Hepatocellular Carcinoma

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Christian Bijan Fink

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gez.:

Dekan: Prof. Dr. med. Nikolaj Klöcker

Erstgutachter: Univ.-Prof. Dr. med. Peter Minko, MBA

Zweitgutachter: Univ.-Prof. Dr. Christoph Roderburg, MHBA

Zusammenfassung

Das hepatozelluläre Karzinom (HCC) zählt weltweit zu den häufigsten krebsbedingten Todesursachen. Die transarterielle Chemoembolisation mit medikamentenfreisetzenden Mikrosphären (DEB-TACE) ist eine etablierte Therapie bei ausgewählten Patienten mit HCC, insbesondere im intermediären Stadium. Die klinischen Verläufe sind jedoch heterogen, und ein verlässlicher früher Marker für den Therapieerfolg fehlt. Etablierte Kriterien wie mRECIST und LI-RADS TR basieren auf einer Bildgebung nach vier bis sechs Wochen und liefern nur eingeschränkte Entscheidungsgrundlagen für eine frühzeitige Therapieanpassung. Ziel dieser retrospektiven monozentrischen Studie war es, zu prüfen, ob frühe Veränderungen in der Computertomographie (CT) – insbesondere die Regression der arteriellen Hypervaskularisation (APHE) und eine frühe Tumorgrößenreduktion – unabhängige Prädiktoren des progressionsfreien Überlebens (PFS) sind. Eingeschlossen wurden 80 HCC-Patienten mit einer CT vor und innerhalb von sieben Tagen nach DEB-TACE. Zwei Radiologen bewerteten Tumorgröße und drei morphologische Merkmale (APHE, Washout, Kapselkontrastierung), aus denen zusätzlich ein kumulativer Regressions-Score (CRS, 0–3) berechnet wurde. Der primäre Endpunkt war das PFS. APHE-Regression nach TACE wurde bei 60,6 % der Patienten beobachtet und war signifikant mit verlängertem PFS assoziiert (HR = 0,49; $p = 0,008$). Auch eine frühe Tumorverkleinerung war ein unabhängiger Prädiktor (HR = 0,61; $p = 0,039$). Während Washout-Regression nur univariat relevant war, zeigte die Regression der Kapselkontrastierung keine prognostische Bedeutung. Der CRS war stufenweise mit dem PFS assoziiert (HR = 0,74; $p = 0,026$). Das finale multivariate Modell (CERM), bestehend aus APHE-Regression und früher Tumorgrößenreduktion, zeigte eine moderate Diskrimination (C-Index 0,65) und trennte die Risikogruppen signifikant (log-rank $p = 0,008$). Die Kalibration zeigte eine günstige Übereinstimmung zwischen vorhergesagten und beobachteten Progressionsrisiken. Die Ergebnisse zeigen, dass frühe morphologische Veränderungen bereits prognostisch verwertbare Informationen enthalten. Unter Berücksichtigung der Limitationen liefert die Studie erste Evidenz für den prognostischen Nutzen der frühen CT nach DEB-TACE und schlägt ein praxisnahes, bildgebungsbasiertes Risikomodell für eine „*response*-gesteuerte“ Therapieplanung beim HCC vor.

Summary

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. Transarterial chemoembolization with drug-eluting beads (DEB-TACE) is an established locoregional treatment for selected patients with HCC, particularly in intermediate-stage disease. However, clinical outcomes after DEB-TACE vary widely, and early prediction of treatment response remains challenging. Established response criteria such as mRECIST and LI-RADS TR rely on imaging four to six weeks post-treatment, limiting their utility for early clinical decision-making. This retrospective single-center study evaluated whether early morphologic changes - particularly regression of arterial phase hyperenhancement (APHE) and tumor shrinkage - can independently predict progression-free survival (PFS). Eighty HCC patients underwent DEB-TACE and CT imaging before and within seven days after treatment. Two radiologists assessed tumor size, APHE, venous washout, and capsule enhancement. Regression was defined as complete disappearance of each morphologic feature and a cumulative regression score (CRS; range 0–3) was calculated. The primary endpoint was PFS. APHE regression was observed in 60.6% of patients and significantly associated with longer PFS (HR = 0.49, $p = 0.008$). Tumor shrinkage, though often minimal, also independently predicted improved outcomes (HR = 0.61, $p = 0.039$). Washout regression was significant only in univariate models; capsule regression was not. The CRS showed a stepwise association with PFS (HR = 0.74, $p = 0.026$). The final multivariable model (CERM), combining APHE regression and tumor shrinkage, showed moderate discrimination (C-index 0.65) and significant risk-group separation (log-rank $p = 0.008$). Calibration was favorable. These results challenge the belief that early post-TACE imaging lacks clinical value. This study supports further evaluation of early CT-based risk stratification after DEB-TACE. CERM complements established response classifications by providing a continuous and interpretable imaging-based risk estimate. Despite its retrospective nature, lack of external validation, and qualitative imaging assessment, the model showed minimal overfitting and good internal calibration. In conclusion, this study provides preliminary evidence for the prognostic utility of early CT after DEB-TACE and proposes a practical candidate imaging-based model for further evaluation of response-guided risk stratification in HCC.

List of abbreviations

AASLD	American Association for the Study of Liver Diseases
ABCR score	Alpha-fetoprotein, Barcelona Clinic Liver Cancer, Child-Pugh, and Response score
ADC	Apparent Diffusion Coefficient
AFP	Alpha-Fetoprotein
ALBI	Albumin–Bilirubin Score
APHE	Arterial Phase Hyperenhancement
ART score	Assessment for Retreatment with TACE score
BCLC	Barcelona Clinic Liver Cancer
CERM	CT-Based Early Response Model
CEUS	Contrast-Enhanced Ultrasound
CI	Confidence Interval
CR	Complete Response
CRS	Cumulative Regression Score
CT	Computed Tomography
CTP	CT Perfusion
DEB-TACE	Drug-Eluting Bead Transarterial Chemoembolization
DECT	Dual-Energy Computed Tomography
DWI	Diffusion-Weighted Imaging
EASL	European Association for the Study of the Liver
ECOG PS	Eastern Cooperative Oncology Group Performance Status
Gd-EOB-DTPA	Gadoxetic Acid Disodium
HAP score	Hepatoma Arterial-Embolization Prognostic Score
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCC-CCA	Combined Hepatocellular-Cholangiocarcinoma
HCV	Hepatitis C Virus
HIF	Hypoxia-Inducible Factor
HPI	Hepatic Perfusion Index
HR	Hazard Ratio
IQR	Interquartile Range

KLCA	Korean Liver Cancer Association
KLCA-NCC	Korean Liver Cancer Association – National Cancer Center
LCSGJ	Liver Cancer Study Group of Japan
LI-RADS, LR	Liver Imaging Reporting and Data System
LI-RADS TR, LR-TR	Liver Imaging Reporting and Data System Treatment Response Algorithm
LP	Linear Predictor
LT	Liver Transplantation
mRECIST	Modified RECIST
MRI	Magnetic Resonance Imaging
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NCC	National Cancer Center
ORR	Objective Response Rate
PACS	Picture Archiving and Communication System
PBC	Primary Biliary Cholangitis
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PMI	Psoas Muscle Index
PR	Partial Response
PSC	Primary Sclerosing Cholangitis
PVA	Polyvinyl Alcohol
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency Ablation
RMST	Restricted Mean Survival Time
SD	Stable Disease
SPSS	Statistical Package for the Social Sciences
TACE	Transarterial Chemoembolization
TERT	Telomerase Reverse Transcriptase
TR	Treatment Response
TSM	Treatment Stage Migration
UK	United Kingdom

USA	United States of America
VEGF	Vascular Endothelial Growth Factor
VIF	Variance Inflation Factor
VPCT	Volume Perfusion CT
WHO	World Health Organization

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1 Introduction

1.1 Clinical Background

1.1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, accounting for approximately 75–85% of all primary liver cancers and representing a major global health burden. In 2020, more than 900,000 new cases of liver cancer were diagnosed globally, and this number is projected to exceed 1.4 million by 2040.(1,2) The incidence of HCC exhibits marked geographic variability. The highest age-adjusted incidence rates occur in East and Southeast Asia as well as sub-Saharan Africa, predominantly due to endemic hepatitis B virus (HBV) infection and aflatoxin exposure. In contrast, incidence in Western countries has been rising steadily over the past two decades, driven by increasing rates of metabolic dysfunction and alcohol-related liver disease.(2) The main etiologic factors for HCC include chronic infection with HBV or hepatitis C virus (HCV), excessive alcohol consumption, and in recent years, increasingly, non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH). NASH has become a predominant risk factor in many high-income countries, particularly among patients with metabolic syndrome, diabetes mellitus, and obesity.(2,3) Unlike virus- or alcohol-related HCC, up to 50% of NASH-related HCC cases occur in the absence of cirrhosis, and current surveillance guidelines do not routinely recommend screening for non-cirrhotic NASH patients, leading to under-recognition and later-stage presentation.(4,5) In low- and middle-income regions, HBV remains the leading cause of HCC, with early-age infection, lack of vaccination coverage, and limited access to antiviral therapy contributing to high disease burden.(2)

HCC is the fourth leading cause of cancer-related mortality worldwide and has a poor overall prognosis, particularly when diagnosed at intermediate or advanced stages. The 5-year survival rate remains below 20% in most real-world cohorts.(3) Prognosis depends on a complex interplay between tumor-related factors (e.g., size, number, vascular invasion), liver function (e.g., cirrhosis stage, bilirubin), and performance status. While curative treatments offer favorable outcomes in early-stage disease, most

patients present at intermediate or advanced stages, where therapeutic options are limited and outcomes remain poor.

Clinically and biologically, HCC is highly heterogeneous. Tumors range from indolent, well-demarcated lesions to aggressive, infiltrative disease with vascular invasion or extrahepatic spread. This heterogeneity is mirrored at the molecular level: recent classifications describe multiple transcriptomic and mutational subclasses, including proliferation vs. non-proliferation subtypes, immune-inflamed vs. immune-excluded phenotypes, and frequent mutations in genes such as TERT promoter, TP53, and CTNNB1.(6,7) However, most of these molecular signatures have not yet led to validated clinical biomarkers or targeted therapies, and their relevance for routine decision-making remains limited. Additionally, HCC often arises in the context of chronic liver disease or cirrhosis, which itself exhibits variability in terms of etiology, fibrosis stage, and functional reserve – further complicating treatment decisions and prognostication.

1.1.2 Staging and Treatment Stratification

The Barcelona Clinic Liver Cancer (BCLC) classification system is the most widely adopted framework for staging HCC, integrating tumor burden, liver function, and Eastern Cooperative Oncology Group-performance status (ECOG PS) to stratify patients into distinct prognostic categories and to guide treatment allocation.(8,9) Patients with intermediate-stage HCC (BCLC B) represent a particularly heterogeneous group, characterized by multinodular tumors, preserved liver function, and good performance status (ECOG PS 0) (Figure 1). They are usually not amenable to resection or ablation, but a subset may be considered for liver transplantation. For this stage, transarterial chemoembolization (TACE) is considered the standard of care according to both EASL and AASLD guidelines.(2,10) Meta-analyses of randomized controlled trials have consistently shown a survival benefit of TACE over best supportive care in this population.(11–13) However, substantial intragroup variability in tumor biology and treatment response has prompted further refinements. The 2022 BCLC update introduced key concepts such as treatment stage migration and untreatable progression, reflecting real-world deviations from the idealized stage-treatment linkage.(8) For instance, TACE may be considered in select patients with early-stage disease who are unsuitable for curative therapies, as well as patients with

liver-dominant advanced disease and preserved liver function.(14–18) Conversely, TACE may be abandoned in intermediate-stage disease if the tumor is infiltrative, extensive, or refractory to prior embolization attempts. In addition, the updated BCLC algorithm subclassifies stage B patients into three categories – transplant-eligible (e.g., via expanded criteria), TACE-eligible, and TACE-unsuitable – facilitating a more individualized approach.(9) Recent proposals such as the “Seven-Eleven Criteria” offer alternative subclassifications of tumor burden within BCLC B by combining lesion number and size, helping to refine TACE eligibility and predict response.(19) Overall, the evolution of the BCLC system highlights a paradigm shift from rigid stage-treatment links toward dynamic and multidisciplinary decision-making, where early response assessment and individualized adaptation of therapy are increasingly emphasized.

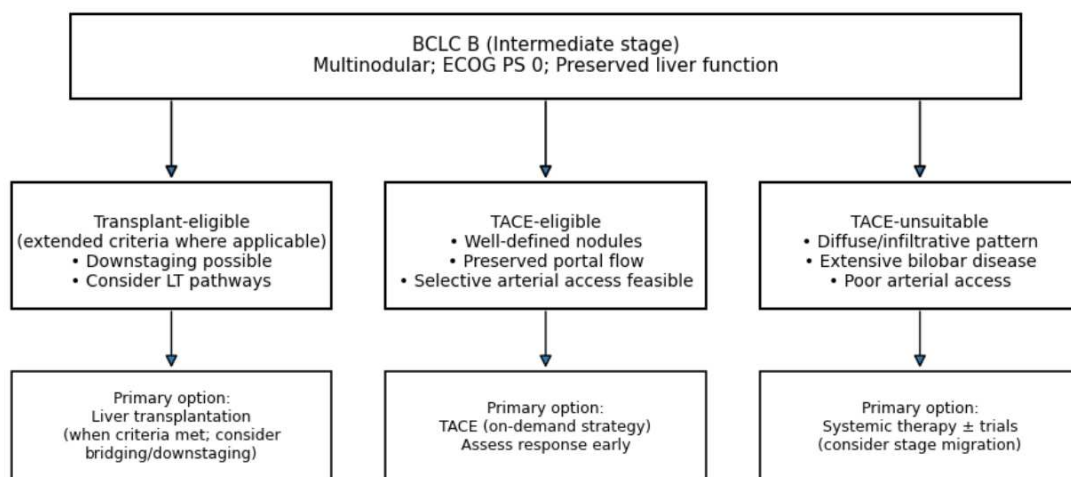


Figure 1. Subclassification of BCLC stage B according to the 2022 BCLC strategy update; based on (8)

1.1.3 Technical principles of TACE

TACE exploits the predominantly arterial blood supply of HCC by delivering chemotherapeutic agents directly into tumor-feeding arteries, followed by embolization to induce ischemia, cytotoxicity, and subsequent tumor necrosis while relatively preserving surrounding liver parenchyma.

Two principal TACE techniques are commonly used: conventional TACE (cTACE) and drug-eluting bead TACE (DEB-TACE). In cTACE, an emulsion of a chemotherapeutic agent (most frequently doxorubicin, epirubicin, or cisplatin) emulsified with iodized oil (Lipiodol®) is injected into tumor-feeding arteries. Depending on operator preference, this is often followed by additional embolization using materials such as gelatin sponge particles or polyvinyl alcohol (PVA) particles, although this step is not mandatory and varies across institutions and geographic regions.(20)

Drug-eluting bead TACE (DEB-TACE), developed to reduce systemic toxicity and enhance local drug delivery, uses embolic microspheres that are preloaded with chemotherapy, most commonly doxorubicin. Microspheres are designed to release the drug in a controlled manner and simultaneously occlude tumor-feeding vessels. The absence of lipiodol in DEB-TACE facilitates post-treatment imaging assessment and reduces interpretative limitations.(20,21)

Comparative studies and meta-analyses have shown no consistent overall survival advantage of DEB-TACE over cTACE in unselected patient populations. However, DEB-TACE may provide higher objective tumor response rate and improved disease control rate in selected subgroups, including patients with nodular HCC, large lesions (> 10 cm), arterioportal shunts, or prior cTACE refractoriness.(21–34) Consequently, the choice of TACE technique should be individualized based on tumor characteristics, liver function and institutional experience.

1.1.4 Outcome Variability and Retreatment Strategies

Response to TACE is influenced by both technical and biological factors. Angiographic endpoints such as the “tree-in-winter” pattern, indicative of complete arterial tumor devascularization, are commonly pursued in cTACE procedures. In DEB-TACE, the focus shifts toward homogeneous bead distribution with minimal reflux, ideally achieved via super-selective catheterization, which enables maximal drug delivery while sparing surrounding parenchyma.(2,35) Well-circumscribed, encapsulated, or nodular HCCs – characterized by smooth margins and arterial hyperenhancement – are more likely to achieve near-complete necrosis and better radiological response to TACE, compared to infiltrative or poorly defined tumors, which tend to respond less favorably and have poorer outcomes.(36,37) This is consistent with the observation that tumor biology, including grade and vascularity, is a major determinant of TACE

response.(38,39) For example, Hung et al. demonstrated that encapsulated tumors showed the highest response and survival rates after both initial and repeat TACE sessions.(40) Repeated TACE procedures may induce arterial remodeling, which may contribute to treatment refractoriness in HCC patients. The concept of ‘TACE failure/refractoriness’ has been specifically defined by the Liver Cancer Study Group of Japan (LCSGJ) and the Japan Society of Hepatology. Their criteria include: (1) two or more consecutive ineffective responses (i.e., lack of objective response or persistent viable tumor after at least two TACE sessions), and (2) the appearance of vascular invasion or extrahepatic spread during or after TACE, among other features.(41,42) This concept has influenced international practice. The AASLD incorporates similar criteria in its 2023 guidance, stating that TACE refractoriness is suggested by more than 50% viable disease after two TACE treatments, new HCC within the treatment zone after two consecutive TACE, lack of tumor marker improvement, or stage migration to advanced HCC (including new vascular invasion or extrahepatic metastases). However, while this concept is widely recognized and has been incorporated into international consensus guidelines, its application remains inconsistent in global clinical practice. Variability exists in how strictly these criteria are applied, and some centers may continue TACE beyond these thresholds, particularly in the absence of alternative therapies or in select patient populations. To mitigate the risk of overtreatment and cumulative hepatotoxicity, an “on-demand” approach to re-TACE has gained favor over fixed retreatment intervals. This strategy advocates that subsequent TACE sessions be guided by objective radiological response rather than protocolized timing, enabling personalized treatment plans that adapt to individual tumor behavior. Given the multifactorial nature of TACE response and the increasing emphasis on dynamic, image-guided decision-making, the role of diagnostic imaging in HCC has expanded far beyond initial detection and staging.

1.1.5 Diagnostic Imaging Modalities in HCC

Accurate imaging is essential for the non-invasive diagnosis of HCC, especially in patients with liver cirrhosis, where histological confirmation is often avoided. According to international guidelines, ultrasound remains the primary tool for surveillance in high-risk populations due to its cost-effectiveness and availability.

However, its sensitivity for early-stage HCC detection is limited, especially in patients with obesity or non-alcoholic steatohepatitis (NASH).(43)

Contrast-enhanced multiphasic CT and MRI represent the diagnostic mainstay for HCC confirmation. These cross-sectional modalities enable visualization of hallmark imaging features, which are required for a definitive diagnosis without histological confirmation in cirrhotic patients.(9) MRI may offer higher sensitivity for small or equivocal lesions, whereas CT remains widely available and standardized.(44–46) In addition to CT and MRI, CEUS has emerged as a valuable adjunct in selected scenarios. It is particularly useful in evaluating indeterminate lesions or in patients with contraindications to iodinated or gadolinium-based contrast agents.(47) However, CEUS remains operator-dependent and is not universally incorporated into major diagnostic algorithms.

The four cardinal imaging hallmarks of untreated HCC include (non-rim) APHE, non-peripheral washout, enhancing capsule, and threshold growth. Among these, APHE represents the most sensitive indicator of viable tumor, reflecting the hallmark arterial neovascularization of HCC. Washout, defined as a relative hypointensity in the portal venous or delayed phase, complements APHE by providing high specificity for HCC. The presence of an enhancing capsule – smooth peripheral rim enhancement in later phases – is supportive but less specific and often seen in other liver lesions as well. Threshold growth, referring to a > 50% increase in tumor diameter within 6 months, can indicate malignant progression but lacks specificity in the absence of other hallmarks. These imaging features form the foundation of diagnostic algorithms such as LI-RADS®, which has been incorporated into major guidelines like those of the AASLD (Figure 2).(2,48) LI-RADS defines LR-5 - definitive for HCC - as the presence of non-rim APHE combined with at least one additional feature: washout, capsule, or threshold growth. However, recent analyses suggest that the diagnostic performance of these features is not uniform: APHE and washout remain the most reliable markers, while capsule enhancement and threshold growth show lower sensitivity and prognostic value.(49–52) The pattern of APHE may also carry prognostic and diagnostic implications. Non-rim APHE is the hallmark imaging feature of typical HCC and forms the cornerstone of non-invasive diagnosis. In contrast, rim APHE is more commonly associated with poorly differentiated tumors, cholangiocarcinoma, or combined HCC-CCA and thus categorized as LR-M in LI-RADS. Therefore, the absence of non-rim APHE or presence of atypical enhancement patterns should prompt careful diagnostic reconsideration.(50)

While these hallmark imaging features form the basis for the non-invasive diagnosis of untreated HCC, therapeutic interventions - particularly TACE - fundamentally alter tumor vascularity and tissue composition. As a result, interpreting post-treatment imaging requires a distinct set of criteria and radiological expectations.

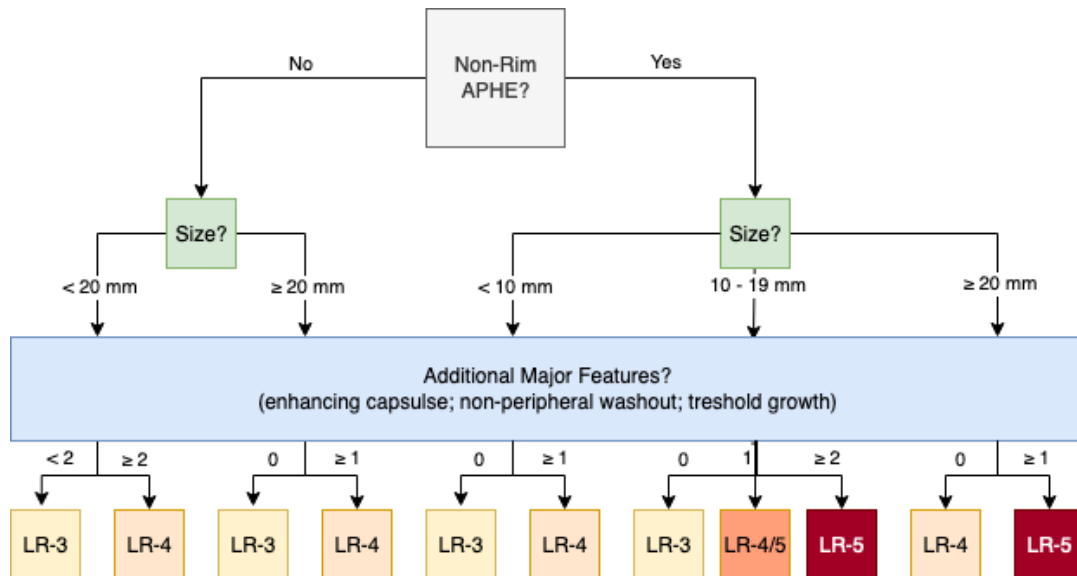


Figure 2. Diagnostic decision tree of LI-RADS v2018 categories LR-3 to LR-5, based on (2)

1.2 Imaging-Based Response Assessment after TACE

1.2.1 Typical Post-Therapeutic Imaging Findings in HCC

Locoregional therapies such as TACE or radiofrequency ablation (RFA) induce characteristic imaging changes in HCC that differ markedly from those seen in untreated lesions.(53) Expected features on CT or MRI include decreased or absent APHE, as well as disappearance of non-peripheral washout and capsule enhancement. In contrast, persistent or newly emerging nodular APHE – particularly when accompanied by washout – indicates residual viable tumor tissue and incomplete treatment response. In cTACE, intratumoral lipiodol retention may obscure enhancement assessment, thereby limiting evaluation of residual viability. Nevertheless, lipiodol distribution itself has been proposed as a surrogate marker of local tumor control, with inhomogeneous deposition, low baseline attenuation, or rapid contrast washout being associated with early recurrence.(54) In DEB-TACE, where no lipiodol is deposited, assessment of vascularity is not confounded, and CT and MRI provide

comparable diagnostic performance in assessing morphologic response, particularly when enhancement-based criteria such as mRECIST or LI-RADS TR are applied.(55) After treatment, peripheral enhancement patterns must be interpreted differently than in untreated lesions. Thin, smooth peripheral enhancement is usually attributable to benign reactive hyperemia or granulation tissue, while irregular or nodular rim enhancement – especially when accompanied by washout – suggests the presence of residual viable tumor.(56,57)

1.2.2 Conventional Response Criteria (RECIST, mRECIST, EASL)

Conventional size-based response assessment systems such as RECIST 1.1 or WHO criteria have limited applicability in evaluating HCC after locoregional therapy. These criteria measure changes in total tumor size but fail to account for treatment-induced necrosis, which is common following TACE and does not necessarily result in lesion shrinkage.(58) To address this limitation, enhancement-based systems were introduced. The European Association for the Study of the Liver (EASL) criteria and the modified RECIST (mRECIST) guidelines both define viable tumor as APHE, allowing for a more accurate estimation of treatment efficacy. mRECIST uses unidimensional measurements of enhancing tumor components and defines objective response based on reductions in the sum of viable tumor diameters. The mRECIST criteria define complete response (CR) as the disappearance of any enhancing tumor tissue, partial response (PR) as a $\geq 30\%$ reduction in the sum of diameters of viable (enhancing) lesions, and progressive disease (PD) as a $\geq 20\%$ increase or the appearance of new lesions. Stable disease (SD) encompasses all responses not meeting these thresholds.(58) The EASL proposed enhancement-based response criteria that quantify the viable tumor as the enhancing portion relative to the total lesion size in cross-sectional imaging. Unlike mRECIST, which requires unidimensional measurement of the viable component, the EASL criteria are based on bidimensional calculations of the enhancing area. This approach may increase sensitivity to small changes in tumor viability but has been criticized for limited reproducibility and lack of standardized measurement protocols.(58) While still cited in several studies, EASL criteria have largely been superseded by mRECIST in most interventional oncology trials.(9) Multiple studies have confirmed that enhancement-based criteria correlate more strongly with clinical outcomes than conventional size-based metrics: Gillmore et al. demonstrated that mRECIST and EASL

response at first follow-up independently predicted overall survival, whereas RECIST 1.1 failed to do so.(59) Similarly, Prajapati et al. found that early response by mRECIST at one month post-TACE was significantly associated with survival, while RECIST and WHO criteria were not.(60)

Despite their prognostic advantages, both mRECIST and EASL are subject to limitations. Accurate identification of APHE can be impaired by imaging artifacts, lipiodol retention, or atypical enhancement patterns. Furthermore, interobserver variability remains an issue, especially in borderline or equivocal lesions. Nevertheless, mRECIST has become the preferred standard in most clinical trials and treatment guidelines due to its simplicity and validated prognostic relevance.

1.2.3 Structured Imaging Algorithms (LI-RADS Treatment Response Algorithm)

To overcome the heterogeneity and ambiguity of conventional response criteria, structured assessment systems like the Liver Imaging Reporting and Data System Treatment Response algorithm (LI-RADS TR) have been developed. The LI-RADS TR algorithm (version 2018) classifies treated lesions into one of four categories:

- LR-TR Nonviable: absence of lesional enhancement or the presence of an expected treatment-specific enhancement pattern without features of viable tumor.
- LR-TR Viable: nodular, mass-like, or thick irregular tissue within or along the margin of the treated lesion showing arterial phase hyperenhancement, washout appearance, or enhancement similar to the pretreatment lesion.
- LR-TR Equivocal: enhancement that is atypical for the expected post-treatment appearance but does not definitively meet criteria for viable disease.
- LR-TR Nonevaluable: treatment response cannot be assessed because of inadequate image quality or an incomplete imaging protocol.

APHE remains the most reliable indicator of residual viable tumor, while washout and pretreatment-like enhancement provide limited additional diagnostic value.(61)

Multiple studies have validated the performance of the LI-RADS TR algorithm in patients undergoing transarterial therapies. Shropshire et al. demonstrated that LI-RADS achieves a high specificity (up to 90%) but only moderate sensitivity (~60%) for predicting incomplete necrosis, with APHE being the dominant imaging feature.(62) In contrast to mRECIST, which only considers APHE, LI-RADS incorporates additional criteria, yet these do not significantly enhance diagnostic accuracy and may complicate

interpretation: Seo et al. found that LI-RADS outperformed mRECIST on CT but not MRI, and highlighted the limitations of the "equivocal" category, which often includes viable tumors and leads to clinical uncertainty.(63) Ram et al. further argued for refinement of the algorithm, emphasizing the need for more dynamic, reproducible response metrics and reducing reliance on ambiguous features such as pretreatment-like enhancement.(64)

Despite these efforts to standardize post-treatment imaging interpretation, conventional criteria and structured imaging algorithms remain imperfect proxies for true histopathologic response. These limitations have prompted growing interest in novel imaging biomarkers and simplified response metrics, particularly those observable in the early post-treatment phase, to improve prognostic accuracy and inform individualized decision-making.

1.2.4 Prognostic Imaging Biomarkers and Emerging Techniques

In recent years, several advanced imaging-based approaches have been proposed to enhance prognostication after TACE. Among these, morphologic regression patterns - such as the early disappearance of APHE, non-peripheral washout, or capsule enhancement - have emerged as potential early indicators of treatment response. Huh et al. emphasized that viable tumor is typically characterized by thick, nodular enhancement with washout, whereas benign post-treatment changes such as thin, smooth rim enhancement should not be misinterpreted as residual disease.(65) Beyond morphologic analysis, radiomics and texture-based methods have gained attention for their ability to quantify tumor heterogeneity and microenvironmental features. Zhao et al. demonstrated that combining intra- and peritumoral MRI radiomics with growth pattern analysis significantly improved prediction of early TACE response, outperforming models based solely on clinical or intratumoral features.(66) Similarly, Liu et al. constructed a radiomics-augmented MRI model that robustly stratified patients into prognostic subgroups with distinct PFS outcomes.(67)

A variety of functional imaging techniques, including diffusion-weighted imaging (DWI), CT perfusion, and PET/CT, have also been explored as early biomarkers of response.(68–71) Despite these advances, many of these techniques remain experimental, and their clinical implementation is challenged by variability in acquisition protocols, lack of standardization, and limited prospective validation. Future

work must focus on harmonizing methodologies and integrating these imaging biomarkers with clinical and laboratory parameters to support personalized treatment adaptation.

1.3 Early Post-TACE Imaging

1.3.1 Existing Evidence for Early Imaging

Most established treatment response criteria recommend imaging 4 to 6 weeks after TACE, assuming that earlier time points may be confounded by inflammation, hemorrhage, or residual contrast media.⁽⁷²⁾ However, such delays can hinder timely therapeutic decision-making, particularly in patients at risk for early progression. Consequently, a small number of studies have explored the prognostic potential of imaging performed within the first 7 days after TACE. One of the few studies investigating early imaging within this time frame was conducted by Shiozawa et al., who performed CEUS within 3 days after DEB-TACE in 32 patients. Enhancement patterns were categorized into four groups, with non-enhancement and peripheral ring enhancement predicting complete response rates of 94.1% and 85.7%, respectively. These patterns also predicted both 1-month and 12-month therapeutic outcomes, highlighting CEUS as a sensitive and reproducible tool for very early response prediction.⁽⁷³⁾ Similarly, Kaufmann et al. investigated the prognostic value of early imaging one day after DEB-TACE using both CEUS and volume perfusion CT (VPCT). In 20 HCC patients, significant reductions in arterial perfusion parameters – including hepatic perfusion index (HPI), arterial liver perfusion, blood volume, and blood flow – were observed exclusively in responders. These changes were strongly predictive of treatment response at 2 and 4 months, with a 40% reduction in HPI serving as a highly accurate cutoff for response prediction. Their findings confirm that meaningful vascular changes occur within 24 hours and may serve as reliable early indicators of therapeutic effect.⁽⁷⁴⁾ Further evidence for the diagnostic value of early CT-based vascular changes was provided by Wimmer et al., who evaluated CT perfusion (CTP) four to seven days after TACE in 15 patients with HCC. While absolute changes in arterial or portal blood flow were not significant, the tumor perfusion index was significantly reduced after TACE, both quantitatively and by visual assessment. Notably, visual PI grading within the first week strongly correlated with residual viability in follow-up CT after one

month. Although designed as a feasibility study, their findings suggest that early vascular regression detectable on perfusion CT may serve as an early surrogate marker of treatment response.⁽⁷⁵⁾ Additional support for the prognostic value of early imaging comes from a prospective MRI study by Kamel et al. in 24 patients with unresectable HCC undergoing TACE. The study demonstrated that both arterial and portal venous enhancement of tumors decreased significantly within 24 hours post-TACE and this reduction persisted through week four. In contrast, increases in apparent diffusion coefficient (ADC) – a marker of necrosis – were delayed, peaking at 1-2 weeks and returning toward baseline by week four. Tumor size did not change significantly at any time point.⁽⁷⁶⁾ These findings underscore that early loss of contrast enhancement reflects immediate devascularization and may serve as a more sensitive early indicator of treatment efficacy. Minami and Kudo reviewed the diagnostic performance of various modalities for early post-TACE imaging. They noted that MRI and CEUS may detect viable tumor earlier than CT, although CT remains widely available and practical, especially in DEB-TACE protocols where Lipiodol does not interfere with contrast enhancement. Their narrative supports the use of early enhancement-based criteria, particularly APHE, as potential early biomarkers, even within the first post-treatment week.⁽⁷⁷⁾ Hur et al. found that dual-energy CT (DECT) with virtual unenhanced and low-keV images offered no diagnostic advantage over conventional multiphasic CT and was prone to artifacts from Lipiodol. This underscores the limitations of current DECT-based methods in the post-embolization setting.⁽⁷⁸⁾ Despite promising results, the available evidence for imaging within the first post-treatment week is extremely limited. Notably, no study to date has provided multivariate, CT-based prognostic modeling of morphologic changes within the first 7 days after DEB-TACE.

1.3.2 CT-Based Early Assessment: Opportunity and Rationale

Despite its widespread availability and routine clinical use, contrast-enhanced CT has received limited attention for response assessment during the first week after TACE. CT offers practical advantages, including broad availability, rapid acquisition, and amenability to standardized multiphasic protocols. In DEB-TACE protocols without lipiodol, residual tumor enhancement is not obscured by intratumoral iodized oil, which may complicate assessment after cTACE. APHE and other morphologic changes can

therefore be assessed directly on early post-treatment CT. Previous reviews have described CT as a feasible and practical modality for post-TACE assessment and have emphasized the importance of distinguishing thin, smooth peripheral enhancement related to post-treatment changes from nodular or mass-like residual enhancement. Nevertheless, reactive hyperemia, inflammation, and granulation tissue during the first post-treatment weeks may complicate image interpretation.^(72,77) Taken together, CT represents a practical modality for first-week assessment after DEB-TACE, but the prognostic significance of morphologic changes observed at this time point remains unresolved. Specifically, it is unclear whether early changes in APHE, washout, capsule enhancement, or tumor size predict progression-free survival. This unresolved question provides the rationale for the present study.

1.4 Methodological Challenges

1.4.1 Conceptual and Technical Hurdles

Imaging biomarker development is challenged by heterogeneity in image acquisition, feature definition, and reader assessment. Differences in scanner platforms, contrast administration and timing, slice thickness, reconstruction algorithms, and post-processing methods can alter the visibility and measurement of imaging features. Inconsistent feature definitions and non-standardized reader assessment may further reduce reproducibility and introduce measurement bias. These dependencies are particularly relevant to radiomics-based approaches. High-dimensional quantitative features are sensitive to acquisition parameters, reconstruction techniques, and segmentation methods. In small datasets with a high feature-to-sample ratio, radiomics models are also susceptible to overfitting and limited transferability across institutions.^(79,80) Reproducible imaging biomarker research therefore requires harmonized acquisition protocols, prespecified feature and endpoint definitions, blinded reader assessment, transparent model development, and appropriate internal and external validation. Without these methodological safeguards, promising findings from individual cohorts may have limited transferability across institutions, scanner platforms, and patient populations.

1.4.2 Endpoint Definition and Circularity Problems

The evaluation of therapeutic efficacy after TACE in HCC frequently relies on imaging-based endpoints such as response rates defined by mRECIST, EASL, or LI-RADS criteria. However, these same imaging features - most notably APHE, washout, or capsule enhancement - are also used as early predictors of treatment success. This dual role raises a conceptual challenge: imaging is simultaneously used as a prognostic tool and as a surrogate endpoint, potentially introducing a circular reasoning bias in both clinical practice and research. Several studies have acknowledged this issue implicitly.⁽⁵⁹⁾ In methodological terms, this corresponds to incorporation bias, a well-recognized problem in radiological research where the test variable is incorporated into the reference standard itself.^(81,82) More explicit critiques have further highlighted the general limitations of surrogate endpoints in oncology and specifically for imaging biomarkers.^(83,84) These considerations emphasize the need for independent clinical endpoints or histopathologic validation.

1.5 Clinical Relevance and Unmet Needs

1.5.1 Clinical Decision Points after TACE

In clinical practice, treatment decisions after TACE must often be made before the conventionally recommended follow-up window of 4–6 weeks. Decisions such as repeating TACE, switching to systemic therapy, or deferring further intervention must therefore rely on early indicators of treatment response. Current guidelines support response-adapted decision-making rather than fixed treatment schedules. For example, international consensus statements and national guidelines recommend reassessment of treatment strategy in the absence of objective response or in the presence of early progression, favoring timely transition to alternative therapies over ineffective repetition of TACE.^(14,18) The prognostic impact of achieving CR after the first TACE session has been emphasized in several retrospective studies. Kim et al. found that initial CR was the strongest predictor of long-term survival, surpassing even best response achieved over multiple sessions. Importantly, the timepoint of CR - early versus delayed - was shown to have an independent influence on prognosis.⁽⁸⁵⁾ These findings support a stratified treatment approach, wherein early responders may continue with TACE

while non-responders are redirected to alternative modalities. Recent guideline updates, such as the 2022 BCLC strategy, have further formalized dynamic treatment concepts such as treatment stage migration and untreatable progression.(8)

Overall, clinical decision-making after TACE increasingly relies on early, response-adapted assessment rather than predefined treatment cycles, highlighting the need for reliable early imaging biomarkers.

1.5.2 Gaps in Current Predictive Strategies

Despite the wide application of radiologic response criteria such as mRECIST and LI-RADS TR, substantial limitations remain with regard to early prognostic assessment after TACE. One major limitation is the categorical nature of these systems, which may oversimplify heterogeneous treatment responses and fail to capture dynamic tumor behavior. Bartnik et al. found that the initial LI-RADS TR response was not independently predictive of overall or time-to-progression survival, with only the “equivocal” category showing independent negative prognostic value.(86) Moreover, mRECIST may overestimate tumor necrosis, as pathological correlation studies have shown residual viable tumor in a substantial proportion of lesions classified as complete response.(87) This underscores the need for refined, quantitative imaging biomarkers beyond dichotomous classifications. Existing response frameworks are also constrained by their reliance on imaging timepoints 4–6 weeks post-TACE, while evidence supporting earlier response assessment remains sparse. In addition, most response systems focus exclusively on imaging findings and do not account for relevant clinical or laboratory parameters such as AFP dynamics, liver function, or tumor biology, which may independently influence prognosis.(2,88)

Together, these limitations point to a gap in current predictive strategies, particularly with respect to early, reproducible, and clinically actionable biomarkers. Addressing this gap requires pragmatic approaches that can be applied in the early post-treatment phase and provide prognostic information beyond conventional response categories.

1.6 Aims of the Study

The primary objective of this study was to investigate whether morphologic features observable on contrast-enhanced CT within one week after DEB-TACE can predict progression-free survival in patients with hepatocellular carcinoma. Specifically, we aimed to:

- Quantify the prevalence and regression of classical imaging hallmarks – non-rim arterial phase hyperenhancement, washout, and enhancing capsule – in early post-treatment CT.
- Evaluate the prognostic relevance of these morphologic changes for progression-free survival.
- Develop and internally validate multivariable prognostic models integrating early imaging findings.
- Compare the prognostic performance of these early models with mRECIST and LI-RADS TR applied to the same early post-treatment CT examinations.

By focusing on accessible and reproducible CT-based biomarkers in the early post-treatment phase, this study seeks to lay the foundation for response-adaptive treatment algorithms and personalized care strategies in patients with HCC undergoing DEB-TACE.

2 Materials and Methods

2.1 Study Design and Population

This retrospective, single-center study included patients diagnosed with HCC who underwent DEB-TACE between June 2014 and April 2021. The institutional ethics committee approved the study (ref. 2023-2630) and waived informed consent. No a priori sample size calculation was performed due to the retrospective design.

Eligible patients had a diagnosis of HCC based on typical imaging features consistent with EASL criteria or histopathologic confirmation, and underwent contrast-enhanced CT both within four weeks before and within seven days after their first DEB-TACE session. Of 107 patients screened, 8 were excluded due to insufficient image quality, 16 due to prior systemic therapy and 3 due to other concurrent malignancies, leaving a final cohort of 80 patients (Figure 3). All patients were treated with DEB-TACE using 100 μm drug-eluting beads (DC Bead™, Biocompatibles UK Ltd) loaded with 50 mg of epirubicin per session. Procedures were performed under fluoroscopic guidance using a standardized protocol and selective catheterization of tumor-feeding arteries.

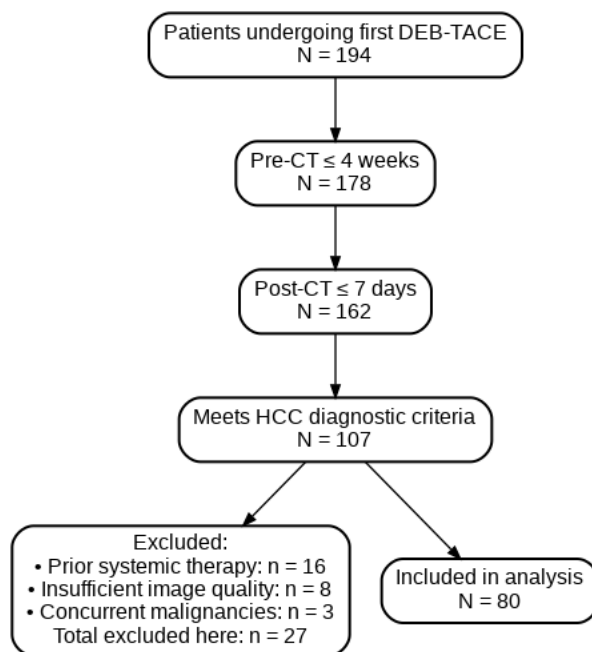


Figure 3. Study flow diagram of patient inclusion and exclusion for the DEB-TACE cohort.

2.2 Clinical and Laboratory Data

Demographic and clinical data were extracted from electronic medical records, including age, sex, tumor size (maximum diameter), presence of extrahepatic metastases, and classification relative to the Milan criteria. Liver function was assessed using the Child-Pugh class and the albumin–bilirubin (ALBI) score. ALBI was calculated as:

$$\text{ALBI score} = \left(\log_{10} \text{bilirubin} \left[\frac{\mu\text{mol}}{\text{L}} \right] \times 0.66 \right) + \left(\text{albumin} \left[\frac{\text{g}}{\text{L}} \right] \times -0.085 \right)$$

Patients were classified into ALBI grades 1 to 3 based on established thresholds. Serum levels of alpha-fetoprotein (AFP), bilirubin, and albumin were recorded prior to TACE. Sarcopenia was assessed by calculating the psoas muscle index (PMI), defined as the total cross-sectional area of both psoas muscles at the L3 vertebral level, normalized to body height (cm^2/m^2), using manual segmentation on axial CT images.

2.3 Imaging Protocol and Analysis

Contrast-enhanced multiphasic CT was acquired before and within seven days after DEB-TACE. All CT examinations were performed on a dual-source multidetector CT system (SOMATOM Definition Flash, Siemens Healthineers, Germany) using a standardized institutional liver protocol. Imaging was acquired as a multiphasic contrast-enhanced CT of the liver, including an unenhanced phase, an arterial phase, and a portal venous phase. Tube voltage was selected automatically using CARE kV with a reference tube voltage of 120 kVp. The reference tube current-time product was 120 mAs with automatic tube-current modulation. Gantry rotation time was 0.5 s, pitch was 0.6, and detector collimation was 128×0.6 mm. Images were reconstructed using a standard soft-tissue convolution kernel and a wide field of view. Axial images were reconstructed with a slice thickness of 2 mm and an increment of 1.6 mm. Additional multiplanar reconstructions were generated in the coronal and sagittal planes with a slice thickness of 3 mm and an increment of 2.4 mm. For the portal venous phase, additional reconstructions were performed using a sharp kernel for abdominal axial

images (2 mm slice thickness, 1.6 mm increment) and sagittal lumbar spine images (3 mm slice thickness, 2.4 mm increment), according to institutional standards. The arterial phase was acquired using bolus tracking with a region of interest placed in the descending aorta. The portal venous phase was acquired with a fixed delay of 55 seconds after contrast injection. Scan direction was craniocaudal for all phases. An iodinated contrast agent (iohexol 300 mg iodine/mL) was administered intravenously via a power injector at a flow rate of 3.0 mL/s. The contrast volume was weight-adapted according to institutional standard operating procedures, typically ranging from 80 to 120 mL. No oral contrast agent was administered. Image evaluation was performed independently by two board-certified radiologists with 5 and 7 years of experience in liver imaging, blinded to patient outcomes. Discrepancies were resolved by consensus. The following HCC-specific morphological features were assessed in both pre- and post-TACE imaging:

- Arterial phase hyperenhancement: non-rim-like enhancement exceeding background liver in the arterial phase.
- Non-peripheral washout: non-peripheral decrease in attenuation compared to the surrounding liver parenchyma in portal venous phase, excluding peripheral-only washout.
- Capsule enhancement: smooth, uniform, peripheral rim of enhancement in portal venous phase.

For each feature, regression was defined as complete disappearance on early post-TACE imaging. Only patients with the respective features present before treatment were included in the analysis for that feature. Tumor size (maximum diameter) was measured on pre- and post-treatment CT. Absolute and relative changes were calculated, and tumor shrinkage was defined as any reduction in size.

In addition to individual features, a Cumulative Regression Score (CRS) was assigned to each patient by counting the number of regressed morphologic features (range 0-3). Only patients with at least one feature present at baseline were included in the CRS analysis.

2.4 Treatment Response Classification

Tumor viability after TACE was further evaluated using two established response systems:

- mRECIST: Response assessment was limited to patients with APHE before TACE. Complete response was defined as disappearance of APHE. Partial response (PR) required at least a 30% decrease in the sum of diameters of enhancing target lesions. Progressive disease (PD) was defined as an increase of at least 20% in the sum of diameters of enhancing lesions or the appearance of new lesions. Stable disease (SD) was defined as any case not qualifying for CR, PR, or PD. Objective response rate (ORR) was defined as the sum of CR and PR.
- LI-RADS Treatment Response (LI-RADS TR) v2018: Lesions were categorized as viable, nonviable, or equivocal.

2.5 Outcome Measure

The primary endpoint of this study was progression-free survival, defined as the time from the initial DEB-TACE to the first radiologically documented progression on follow-up imaging. Patients without documented radiological progression were censored at the date of their last available imaging follow-up. Death without prior documented radiological progression was not counted as an event.

2.6 Statistical Analysis

All statistical analyses and visualization were conducted using SPSS (version 29.0.2.0, IBM Corp., Armonk, NY, USA) and Python (v3.10.12, pandas, numpy, scipy, lifelines, matplotlib). Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were tested for normality using the Shapiro-Wilk test and compared with the independent t-test or Mann-Whitney U test, depending on data distribution. Paired comparison of morphological imaging features

was analyzed using McNemar's test. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient. PFS was analyzed using the Kaplan-Meier method and compared between groups using the log-rank test. Univariate Cox proportional hazards models were constructed to assess the association between individual clinical, laboratory, and imaging variables and PFS. Variables with clinical relevance and/or statistical significance in univariate testing were included in multivariate Cox regression models. The final multivariate model was used to calculate a linear predictor (log-hazard). Progression risks at 90 and 180 days were derived using the cumulative baseline hazard function. Model performance was assessed by Harrell's concordance index (C-index), with internal validation via 1,000 bootstrap iterations to correct for potential overfitting. Calibration was visually evaluated using calibration curves at 90, 147, and 180 days. Patients were further stratified into high- and low-risk groups based on the median model-derived relative risk score $\exp(LP)$, and Kaplan-Meier survival analysis was performed to compare outcomes between strata. A two-sided p -value < 0.05 was considered statistically significant for all analyses.

3 Results

3.1 Patient characteristics

A total of 80 patients diagnosed with hepatocellular carcinoma (HCC) were included in this study. The median age was 69.5 years (range: 35–90), with a predominance of male patients (n = 55, 68.8%). The most frequent underlying etiologies of liver cirrhosis were hepatitis C virus infection (n = 27, 33.8%) and alcohol-related liver disease (n = 17, 21.3%), including cases in combination with other causes. At baseline, 37 patients (46.3%) exceeded the Milan criteria. Extrahepatic metastases were present in 8 patients (10.0%). Child-Pugh classification was available in 63 patients, of whom 46 had Child-Pugh class A, 16 class B, and one class C. Baseline patient characteristics are summarized in Table 1.

Table 1. Baseline patient characteristics

Characteristic	Category	N (%)
Age	Median (range)	69.5 (35-90)
Sex	Male	55 (68.8%)
	Female	25 (31.2%)
Pathogenesis	HCV	27 (33.8%)
	Alcohol-related	17 (21.2%)
	Cryptogenic	13 (16.2%)
	HBV	9 (11.2%)
	Nutritive-toxic	7 (8.8%)
	NASH	5 (6.2%)
	HDV	2 (2.5%)
	Hemochromatosis	2 (2.5%)
	PBC	2 (2.5%)
	Other	3 (3.6%)
Milan criteria	Within	43 (53.8%)
	Beyond	37 (46.2%)
Extrahepatic metastases	No	72 (90.0%)
	Yes	8 (10.0%)
Child-Pugh class	A	46 (73.0%)
	B	16 (25.4%)
	C	1 (1.6%)

3.2 Survival Outcome

Kaplan-Meier analysis yielded an estimated median PFS of 147 days (95 % CI: 101-193 days) (Figure 4). During follow-up, 68 of 80 patients (85.0%) experienced radiologically documented progression. Patients without an event were censored at the date of their last imaging follow-up. Median PFS was 155 days in patients with Child-Pugh class A and 144 days in patients with Child-Pugh class B. The single patient with Child-Pugh class C was not analyzed as a separate subgroup.

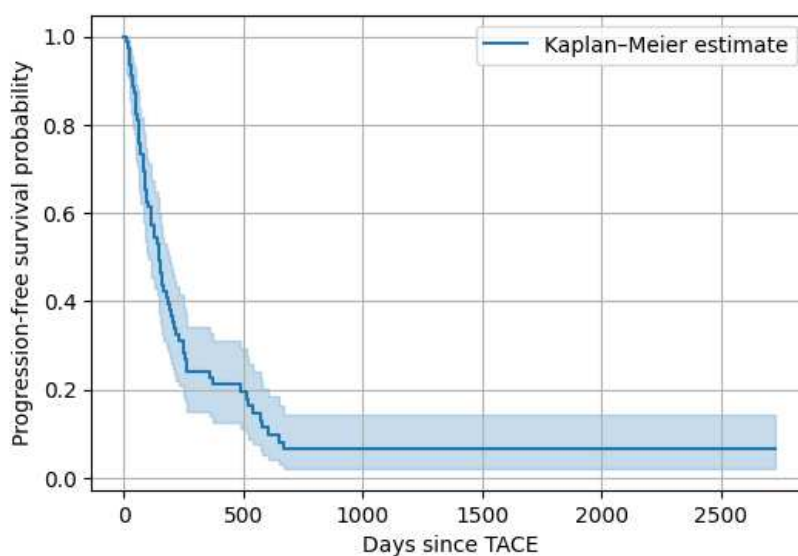


Figure 4. **Kaplan-Meier curve showing PFS after TACE.** The estimated median PFS was 147 days (95% CI: 101-193 days).

3.3 Laboratory Values and Clinical Correlates

Baseline laboratory parameters and their clinical correlates are summarized in Table 2. AFP correlated positively with baseline tumor size ($\rho = 0.30$, $p = 0.009$). Median PMI was significantly higher in men than women ($p < 0.001$). Bilirubin and albumin correlated with Child-Pugh class as expected. None of these parameters, including AFP, bilirubin, albumin, ALBI score, Child-Pugh class, or PMI, showed a significant association with PFS.

Table 2. *Laboratory values and clinical correlates*

Variable	Median (IQR) / Distribution	Additional correlations
Bilirubin (mg/dL)	0.93 (0.57-1.23)	Positive correlation with Child-Pugh ($\rho = 0.47$, $p < 0.001$)
Albumin (g/dL)	3.70 (3.50-4.10)	Negative correlation with Child-Pugh ($\rho = -0.33$, $p = 0.003$)
ALBI score	-2.42 (-2.85 to -2.20)	Grade 1: 28 (35.0%); Grade 2: 49 (61.3%); Grade 3: 3 (3.8 %)
AFP ($\mu\text{g/L}$)	8.60 (4.40-72.30)	Positive correlation with tumor size ($\rho = 0.30$, $p = 0.009$); $\geq 200 \mu\text{g/L}$ in 12 (16.0%)
PMI (cm^2/m^2)	5.80 (4.43-6.82)	Higher in men than women (6.38 vs. 4.43; $p < 0.001$)

3.4 Baseline Tumor Features and Pre-TACE Imaging

The median baseline tumor size was 2.8 cm (IQR: 2.0–5.1 cm). Larger baseline tumor size was associated with shorter PFS in univariate Cox regression (HR = 1.15, 95% CI: 1.07–1.24, $p < 0.001$). Macroscopic vascular invasion was also associated with shorter PFS (HR = 7.28, 95% CI: 2.09–25.29, $p = 0.002$), although it was present in only three patients. Patients beyond Milan criteria had numerically shorter PFS, but the difference was not statistically significant (log-rank $p = 0.303$).

3.5 Morphologic Response on Early Post-TACE Imaging

Early follow-up CT imaging performed within a median of 1 day after DEB-TACE (IQR: 1–2 days) demonstrated marked changes in multiple morphologic tumor features. Tumor size was evaluated before and after TACE in all 80 patients. The median pre- and post-interventional maximum tumor diameters were both 2.8 cm. The median change in maximum diameter was 0.0 cm (IQR: –0.2 to +0.3 cm), and the median relative change was 0.0% (IQR: –5.1% to +6.8%). No significant size reduction was observed at the group level (Wilcoxon signed-rank test, $p = 0.29$). Regression of APHE, washout and capsule enhancement was defined as complete disappearance of the respective feature on early post-TACE CT. Among patients with the feature present at

baseline, complete regression was observed for APHE in 43 of 71 patients (60.6 %), washout in 39 of 57 patients (68.4 %), and capsule enhancement in 24 of 27 patients (88.9 %; Table 3, Figure 5). Intraindividual changes for all three parameters were statistically significant (all McNemar $p < 0.001$).

Table 3. Presence and regression of APHE, washout and capsule enhancement.

Feature	Present before TACE	Present post-TACE	Regression Rate (%)
APHE	71	28	60.6
Washout	57	18	68.4
Capsule Enhancement	27	3	88.9

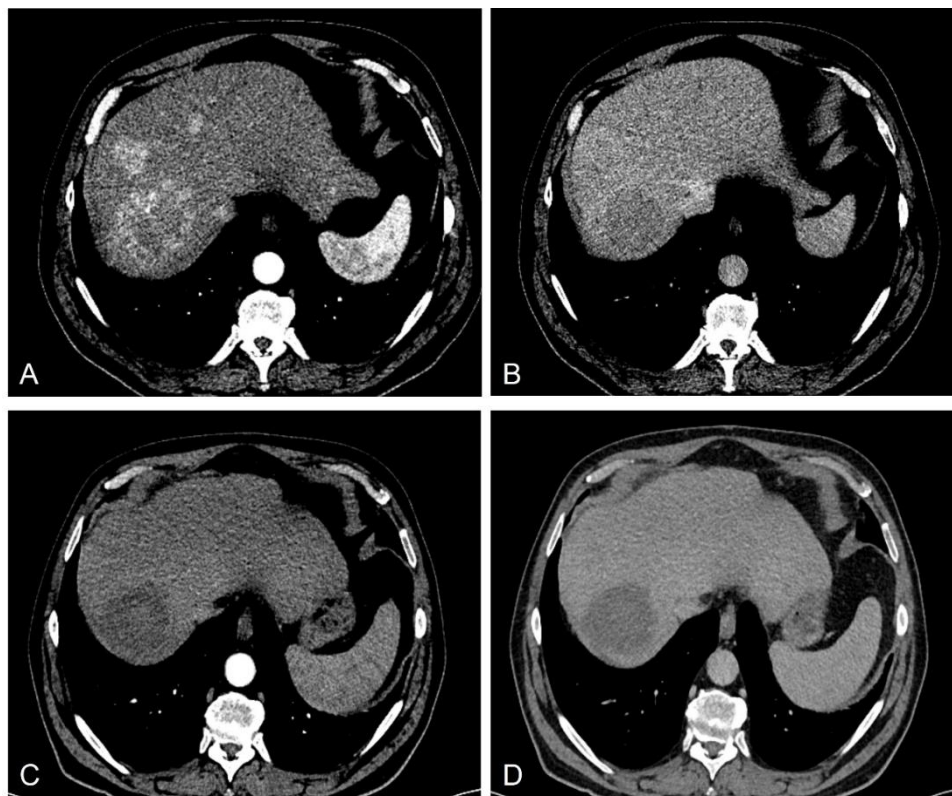


Figure 5. Early morphologic changes on contrast-enhanced CT after DEB-TACE. Axial CT images of a patient with HCC before (A, B) and within 1 day after DEB-TACE (C, D). Baseline imaging shows APHE (A) and venous washout (B), which completely resolve on early post-TACE CT (C, D).

Regression of APHE was significantly associated with regression of non-peripheral washout ($p < 0.001$, Chi-squared test). No significant association was found between regression of APHE and capsule enhancement ($p = 0.679$), nor between regression of washout and capsule enhancement ($p = 1.000$).

Regression of APHE and washout was significantly associated with smaller baseline tumor size ($p < 0.001$ and $p = 0.003$, respectively, Mann-Whitney U test) and post-TACE tumor size ($p < 0.001$ and $p = 0.001$, respectively). No such association was observed for capsule regression ($p = 0.463$ for baseline and $p = 0.354$ for post-TACE size). In addition, regression of APHE and washout was significantly correlated with greater tumor shrinkage ($p = 0.013$ and $p = 0.041$), while capsule regression showed no association ($p = 1.000$).

3.5.1 Cumulative Regression Score

In addition to analyzing individual imaging features, a cumulative assessment of morphologic regression was performed. For each patient, the number of regressed features among APHE, non-peripheral washout, and capsule enhancement was determined. This count was summarized as the CRS, ranging from 0 (no regression) to 3 (regression of all features). Among the 76 patients with at least one evaluable morphologic feature, 18 (23.7%) showed no regression (CRS = 0), 21 (27.6%) demonstrated regression of one feature, 26 (34.2%) of two features, and 11 patients (14.5%) exhibited regression of all three evaluated features (Figure 6).

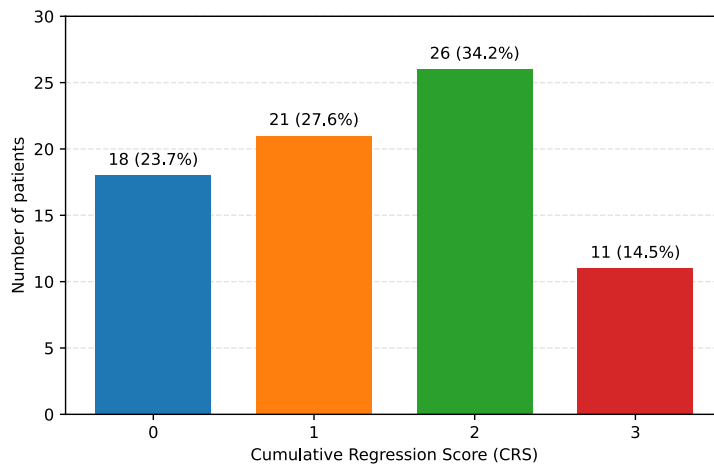


Figure 6. Bar chart showing the distribution of CRS after TACE. The score reflects the number of regressed imaging features (APHE, washout, capsule enhancement).

3.5.2 Objective Response Rate based on early mRECIST

Objective response according to mRECIST criteria was assessable in 71 out of 80 patients (88.8%), based on the availability of pre- and early post-treatment imaging and the presence of measurable APHE on baseline scans. In 9 patients (11.2%), mRECIST evaluation was not possible due to the absence of APHE in pre-TACE imaging, which precluded the definition of a measurable target lesion. Among the 71 evaluable patients, 43 (60.6%) achieved a complete response and 28 (39.4%) showed a partial response on the early post-TACE CT scan. No patients were classified as having stable disease or progressive disease at this early timepoint. Consequently, the objective response rate (ORR; CR + PR) in the assessable cohort was 100%.

3.5.3 LI-RADS TR

In addition to individual morphologic features, we assessed treatment response using the LI-RADS Treatment Response algorithm. Among 76 patients with available LI-RADS TR assessment, 47 (61.8%) were categorized as LR-TR Nonviable and 29 (38.2%) as LR-TR Viable on early post-TACE imaging. No cases were classified as LR-TR Equivocal.

3.6 Prognostic Value of Early Post-TACE Morphologic Changes

3.6.1 Tumor Size Reduction

Larger post-TACE tumor size was associated with shorter PFS in univariate Cox regression (HR = 1.17, 95% CI: 1.10–1.25, $p < 0.001$). However, this association was no longer statistically significant after adjustment for baseline tumor size and either extrahepatic metastasis or albumin ($p = 0.074$ and $p = 0.085$, respectively). Any measurable tumor shrinkage was observed in 30 patients and was associated with longer PFS than no shrinkage in 50 patients (HR = 0.50, 95% CI: 0.30–0.83, $p = 0.007$). This association remained significant in both adjusted multivariate models (HR = 0.61, $p = 0.039$, and HR = 0.60, $p = 0.030$; Table 4). When analyzed continuously, greater tumor shrinkage was also associated with longer PFS (HR = 0.73, 95% CI: 0.54–0.99, $p =$

0.040).

Table 4. Multivariate Cox regression models assessing the prognostic value of early tumor size parameters after TACE, adjusted for baseline tumor size and either extrahepatic metastasis or albumin.

Model	Variable	HR	95% CI	p-value
1a	Size post-TACE	1.32	0.97-1.80	0.074
	Size pre-TACE	0.86	0.63-1.18	0.350
	Metastasis	2.85	1.23-6.61	0.014
2a	Tumor size reduction	0.61	0.38-0.97	0.039
	Size pre-TACE	1.15	1.07-1.23	<0.001
	Metastasis	2.46	1.07-5.69	0.035
1b	Size post-TACE	1.30	0.96-1.76	0.085
	Size pre-TACE	0.89	0.55-1.21	0.449
	Albumin	0.69	0.42-1.14	0.148
2b	Tumor size reduction	0.60	0.37-0.95	0.030
	Size pre-TACE	1.16	1.09-1.24	<0.001
	Albumin	0.68	0.41-1.13	0.132

3.6.2 APHE Regression

Among 71 patients with APHE at baseline, APHE regression was associated with significantly longer PFS (log-rank $p = 0.007$; Figure 7). In univariate Cox regression, APHE regression was associated with a lower hazard of progression (HR = 0.49, 95% CI: 0.28–0.83, $p = 0.008$).

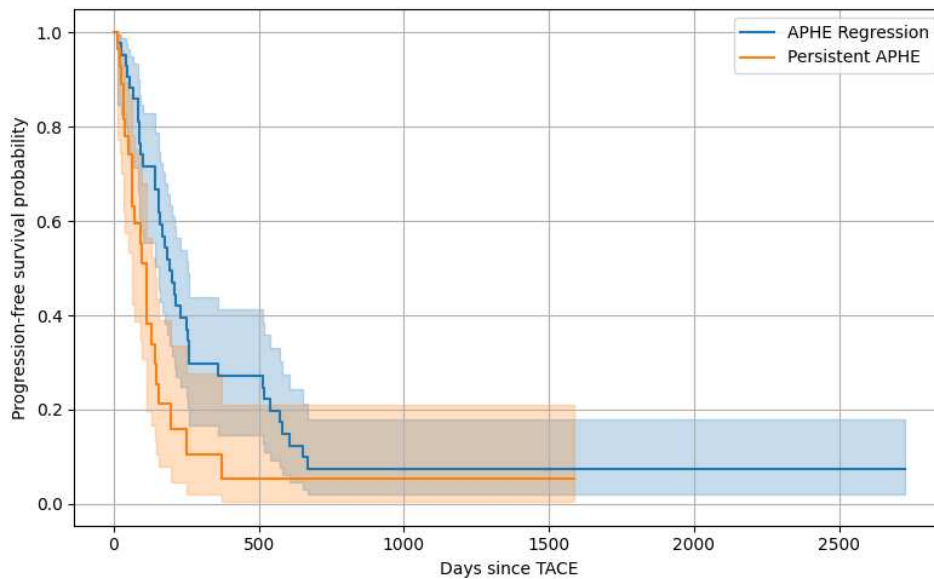


Figure 7. **Kaplan–Meier analysis of PFS according to APHE regression among patients with APHE at baseline.** Patients with APHE regression had significantly longer PFS than those with persistent APHE (log-rank $p = 0.007$).

3.6.3 Washout Regression

Among 57 patients with washout at baseline, washout regression was associated with significantly longer PFS (log-rank $p = 0.003$; Figure 8). In univariate Cox regression, washout regression was associated with a lower hazard of progression (HR = 0.41, 95% CI: 0.22–0.76, $p = 0.005$).

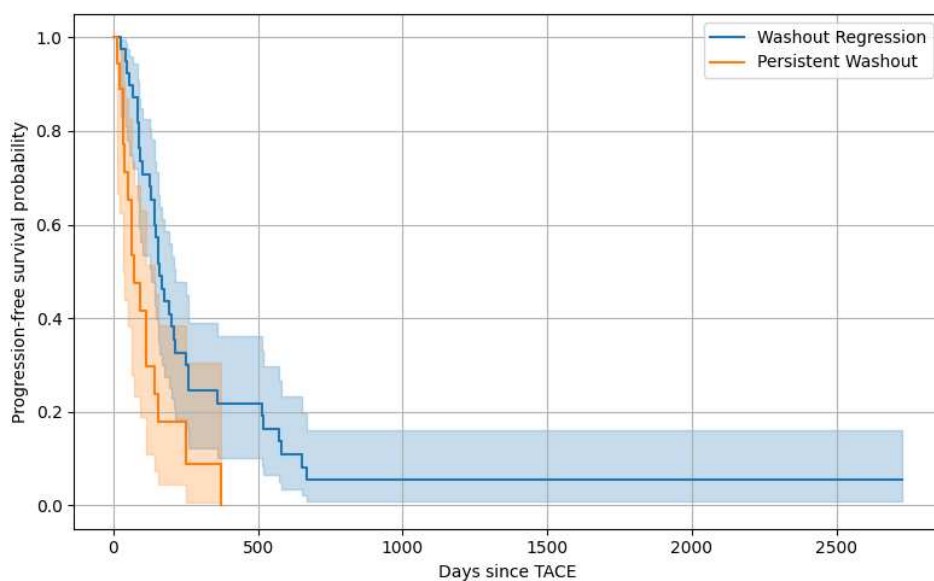


Figure 8. **Kaplan–Meier analysis of PFS according to washout regression among patients with washout at baseline.** Patients with washout regression had significantly longer PFS than those with persistent washout (log-rank $p = 0.003$).

3.6.4 Capsule Enhancement Regression

Capsule enhancement regression was not significantly associated with PFS; interpretation was limited by the small number of patients with persistent capsule enhancement ($n = 3$).

3.6.5 Cumulative Regression Score

Among 76 patients with at least one evaluable morphologic feature, PFS increased stepwise with increasing CRS. Kaplan-Meier analysis demonstrated significant separation between the four CRS groups (log-rank $p = 0.021$; Figure 9). When modeled continuously, each additional regressed feature was associated with a 26% reduction in the hazard of progression (HR = 0.74, 95% CI: 0.57–0.97, $p = 0.026$). In categorical analysis with CRS = 0 as the reference, all higher CRS categories were associated with significantly lower hazards of progression (Table 5).

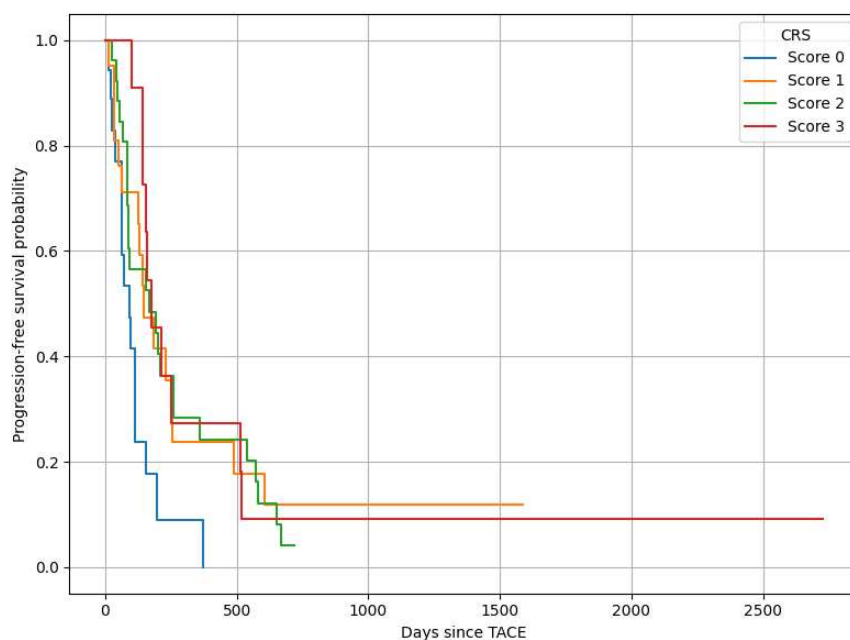


Figure 9. Kaplan–Meier analysis of PFS according to the CRS, which was calculated by summing the number of regressed features (APHE, washout, capsule enhancement) among those present at baseline. Patients with higher CRS showed progressively longer PFS. The difference between CRS groups was statistically significant (log-rank $p = 0.021$).

Table 5. Association between CRS and PFS. PFS was analyzed across score categories using Kaplan-Meier and Cox regression models. HRs are reported for each category compared to patients with no regressed features (CRS = 0).

CRS	N	HR vs. 0	95% CI	P
0	18	Ref	-	-
1	21	0.40	0.20-0.83	0.014
2	26	0.42	0.22-0.82	0.010
3	11	0.36	0.16-0.81	0.014

3.6.6 mRECIST Response

Among 71 evaluable patients, complete response according to early mRECIST was associated with longer PFS than partial response (log-rank $p = 0.007$, Figure 10). In univariate Cox regression, complete response was associated with a lower hazard of progression (HR = 0.49, 95% CI 0.29–0.83, $p = 0.009$).

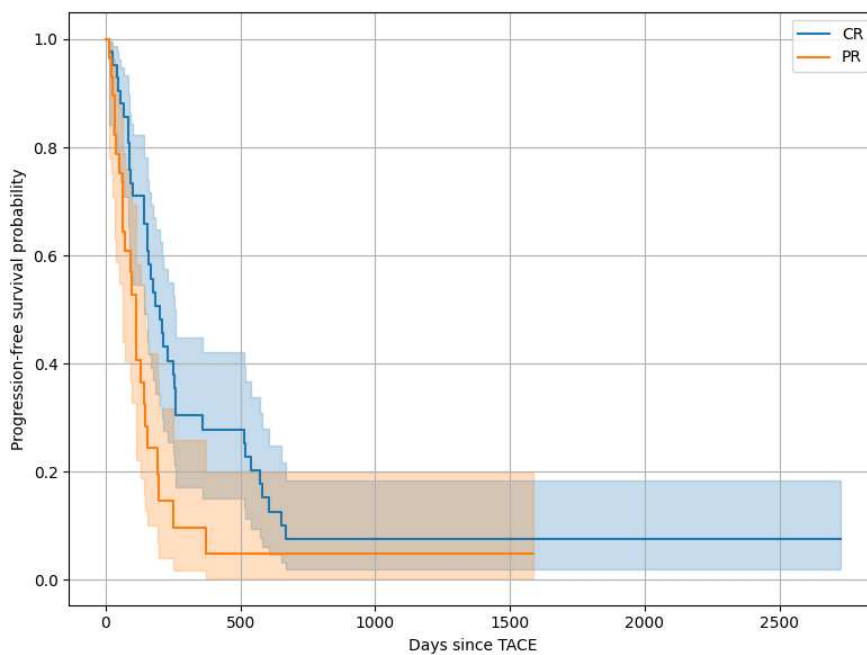


Figure 10. Kaplan–Meier curves comparing PFS between patients with CR and PR based on early mRECIST assessment. Patients achieving CR showed significantly longer PFS (log-rank $p = 0.007$).

3.6.7 LI-RADS TR

Patients classified as LR-TR Nonviable had significantly longer PFS than those classified as LR-TR Viable (log-rank $p = 0.016$, Figure 11). In univariate Cox regression, LR-TR Nonviable response was associated with a lower hazard of progression (HR = 0.53, 95% CI: 0.32–0.90, $p = 0.026$).

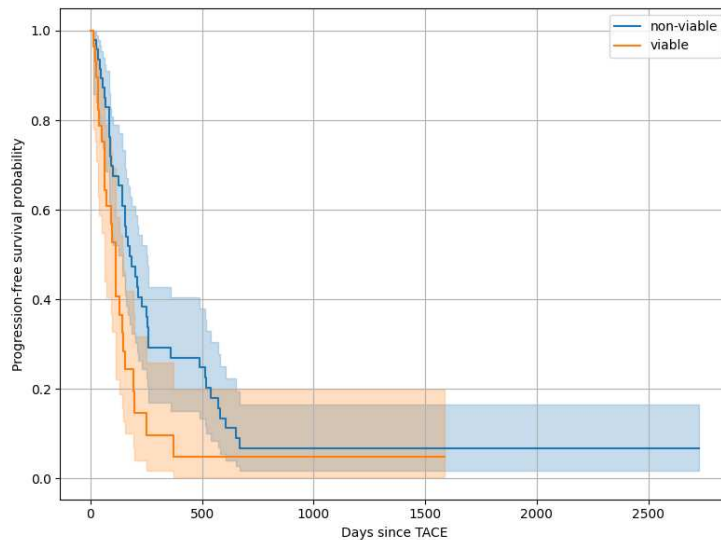


Figure 11. Kaplan–Meier survival analysis of PFS stratified by LI-RADS TR category. Patients with LR-TR Nonviable lesions showed significantly longer PFS compared to those with LR-TR Viable (log-rank $p = 0.016$).

3.7 Development and Validation of Prognostic Models for Progression-Free Survival

3.7.1 Identification of Candidate Variables by Univariate Cox Regression

To identify independent predictors of PFS, all available clinical, imaging, and laboratory variables were first assessed in univariate Cox regression analyses. Statistically significant variables were considered eligible for inclusion in multivariate models. Variables with significant and nonsignificant univariate associations are summarized in Appendix Tables A1 and A2, respectively.

3.7.2 Key Findings from Multivariate Modeling

Several multivariable Cox regression models were constructed across imaging, tumor-burden, biological, and liver-function domains. Among the imaging-only candidate models, M6a – combining APHE regression and continuous tumor shrinkage – was selected as the parsimonious CT-based early response model (CERM) based on statistical performance and clinical interpretability. Full model specifications and results are presented in Appendix Tables A3 and A4.

3.7.3 CT-based Early Response Model

Model M6a, hereafter referred to as CERM, was selected for further validation based on statistical performance and clinical interpretability. In this model, APHE regression was an independent predictor of prolonged PFS (HR = 0.49, 95% CI: 0.29-0.84, $p = 0.009$), while tumor shrinkage showed a non-significant trend (HR = 0.76, 95% CI: 0.54-1.06, $p = 0.107$). The model achieved a global p -value of 0.012 and Harrell's C-index of 0.65. Calibration curves for CERM were generated at 90, 147, and 180 days (Figure 12). The calibration slope was 1.20 at day 90, 1.55 at day 147, and 1.01 at day 180, with corresponding calibration intercepts of -0.08 , -0.28 , and -0.03 , respectively. Visual inspection of the calibration plots showed good agreement between predicted and observed progression risks, particularly at 180 days. Internal bootstrap validation of CERM indicated minimal optimism (apparent C-index = 0.646; mean optimism 0.006; optimism-corrected C-index = 0.639). Kaplan–Meier analysis based on the model-derived relative risk score $\exp(LP)$ showed a significant separation between low- and high-risk patients. Risk groups were defined using the median relative risk score $\exp(LP)$ of 0.781, resulting in a nearly equal distribution (36 vs. 35 patients). The high-risk group exhibited significantly shorter PFS compared to the low-risk group (log-rank $p = 0.008$, Figure 13).

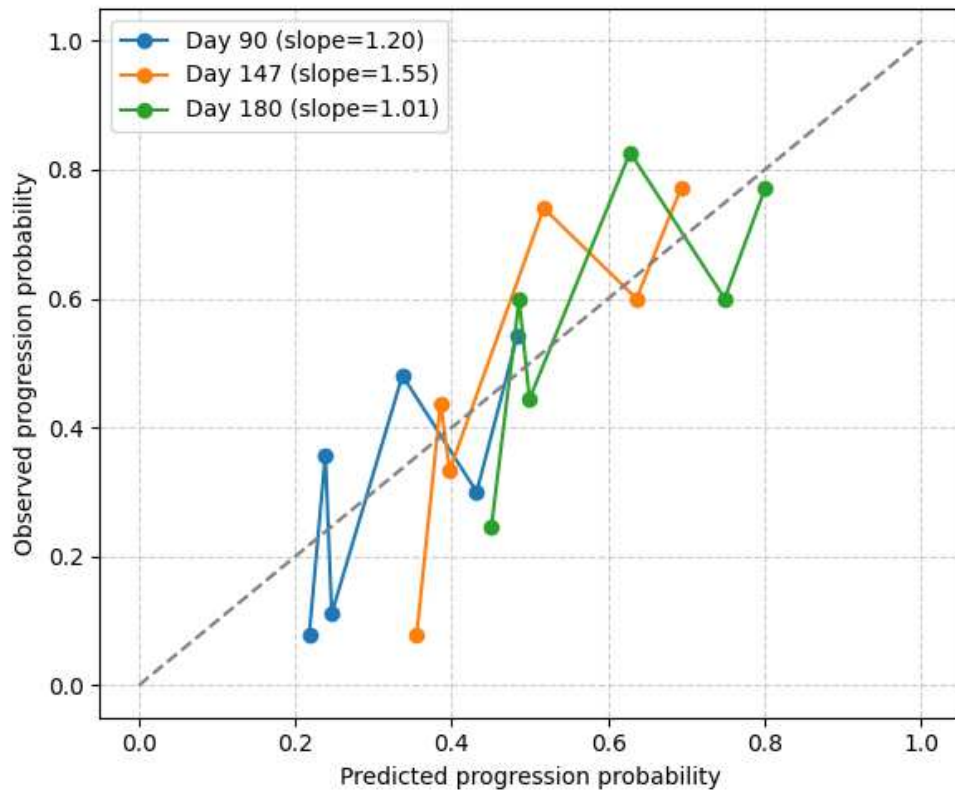


Figure 12. Calibration curves for CERM at 90, 147 and 180 days.

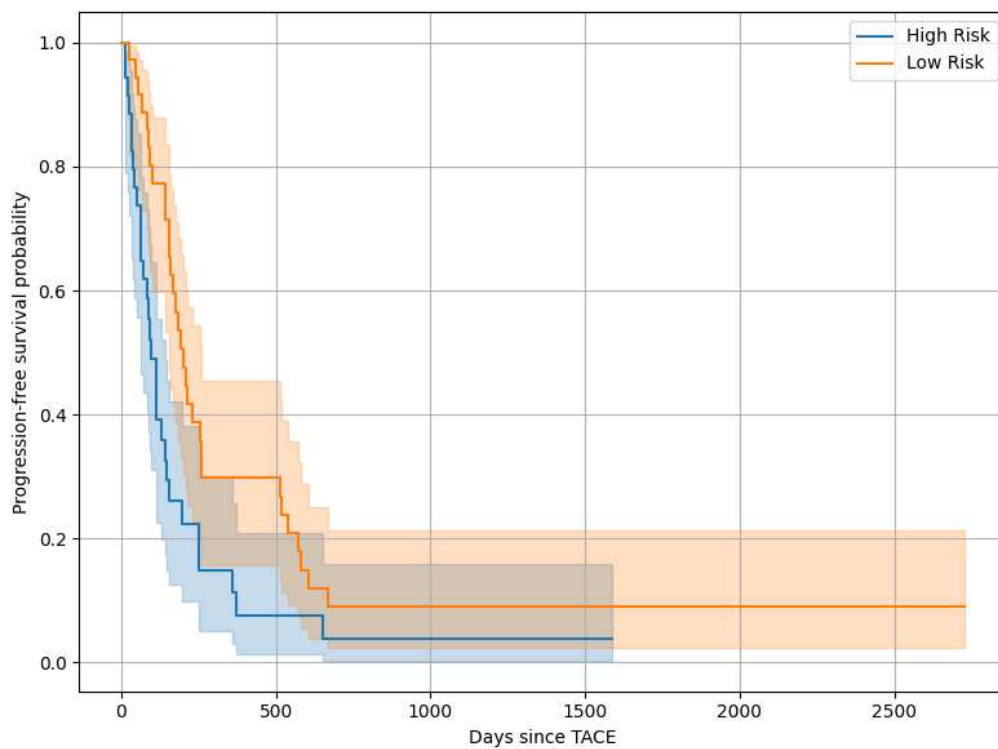


Figure 13. Kaplan-Meier survival curves comparing high- vs. low-risk groups based on the CERM-derived relative risk score $\exp(LP)$. Patients were stratified using the median score of 0.781. Shaded areas represent 95% confidence intervals.

Restricted mean survival time (RMST) was used to quantify the average PFS in the high- and low-risk groups defined by CERM. At 90 days, the low-risk group showed a mean survival of 83.9 days compared to 68.1 days in the high-risk group. This difference increased at 147 days (124.5 vs. 92.7 days) and further at 180 days (145.5 vs. 99.9 days). The predictiveness curve for CERM demonstrated a relatively wide distribution of predicted risk scores, with a steeper increase beyond the 60th percentile (Appendix, Figure A1).

3.7.4 Implementation of a Risk Prediction Formula

To enable practical application of the CERM, a formula-based risk calculator was implemented based on the Cox proportional hazards model. The tool estimates the individual probability of progression by 90 and 180 days following TACE. Risk-group stratification was based on mean-centered relative risk scores derived from the fitted Cox model. For calculation of absolute progression risks, the model was expressed in an equivalent uncentered parameterization. The uncentered linear predictor was calculated as follows:

$$LP = -0.7088 \times APHE - 0.2762 \times Tumor\ Shrinkage\ [cm]$$

APHE regression was coded as 1 and persistent APHE as 0; tumor shrinkage was calculated as the pre-TACE minus the post-TACE maximum diameter in centimeters, with positive values indicating a reduction in tumor size.

The estimated probability of progression by day t was calculated as follows:

$$Risk_t = 1 - \exp(-H_0(t) \times \exp(LP))$$

where $H_0(t)$ denoted the baseline cumulative hazard at day t . The corresponding estimates were:

- $H_0(90) = 0.5584$
- $H_0(180) = 1.3321$

A lookup table for typical patient values is provided (Table 6).

Table 6. Predicted 90- and 180-day progression risk based on APHE response (binary) and tumor shrinkage (in cm) according to CERM.

APHE Response	Tumor Shrinkage (cm)	Predicted Risk at 90d (%)	Predicted Risk at 180d (%)
0	0	42.8	73.6
0	0.5	38.5	68.7
0	1.0	34.5	63.6
0	1.5	30.9	58.5
0	2.0	27.5	53.5
0	2.5	24.4	48.7
0	3.0	21.6	44.1
1	0	24.0	48.1
1	0.5	21.3	43.5
1	1.0	18.8	39.2
1	1.5	16.6	35.2
1	2.0	14.6	31.4
1	2.5	12.9	28.0
1	3.0	11.3	24.9

3.7.5 Comparison of CERM with Established Criteria and Single Predictors

To evaluate the incremental value of CERM, its performance was compared with individual imaging parameters and established criteria (APHE regression, tumor shrinkage, mRECIST, LI-RADS TR, and the Cumulative Regression Score).

As shown in Table 7, CERM achieved the highest Harrell's C-index among the evaluated imaging-based approaches. Its discrimination was moderate and supported by favorable calibration and minimal optimism on internal bootstrap validation.

Table 7. Discrimination of CERM compared with individual imaging predictors and established response criteria, assessed using Harrell's C-index.

Model	Harrell's C-index
CERM	0.646
APHE Regression	0.600
Tumor Shrinkage	0.614
mRECIST	0.600
LI-RADS TR	0.585
CRS	0.605

4 Discussion

4.1 Main Findings and Comparison to Existing Literature

This study provides novel evidence that early morphologic changes on contrast-enhanced CT - particularly APHE regression and tumor shrinkage - carry prognostic value in patients with HCC undergoing DEB-TACE. These findings challenge the traditional assumption that post-treatment imaging within the first week is unreliable, and highlight the potential of structured, enhancement-based evaluation for early response assessment.

Among all evaluated imaging parameters, APHE regression emerged as the single strongest prognostic feature. Patients showing APHE regression exhibited significantly improved PFS (HR = 0.49, $p = 0.008$), a finding that remained robust in multivariable modeling. This observation is consistent with earlier work indicating the superiority of enhancement-based metrics over size-based metrics in the assessment of treatment response after TACE. For example, Gillmore et al. demonstrated that viable tumor enhancement is more strongly associated with outcome than conventional RECIST criteria.⁽⁵⁹⁾ Similarly, Polikoff et al. identified APHE as the most sensitive indicator of viable tumor following locoregional therapy, outperforming both washout and capsule appearance.⁽⁶¹⁾ Evidence from early post-treatment imaging further supports the biological relevance of vascular regression. Kaufmann et al. demonstrated that both CEUS and VPCT can detect marked reductions in tumor perfusion parameters as early as 24 hours post-DEB-TACE.⁽⁷⁴⁾ Kamel et al. showed that contrast enhancement on MRI declines markedly within the first 24 hours after cTACE, whereas diffusion changes and tumor shrinkage occur later and less consistently.⁽⁷⁶⁾ Wimmer et al. demonstrated that tumor perfusion index measured via CT perfusion significantly declined within 4–7 days after TACE, and that visual grading of residual perfusion was highly predictive of tumor viability in follow-up imaging.⁽⁷⁵⁾ Together, these findings reinforce the concept that early devascularization is a primary imaging correlate of treatment efficacy and support the prognostic relevance of APHE loss observed on early CT in our cohort.

Early tumor shrinkage, although less pronounced at this time point, was also independently associated with improved PFS (HR = 0.61, $p = 0.039$). This aligns with the broader concept that morphologic regression reflects tumor sensitivity to embolization. Tamandl et al. demonstrated that tumor shrinkage assessed 4–8 weeks after TACE independently predicted survival, with a $\geq 50\%$ volume reduction associated with significantly improved outcomes.(89) In contrast, our data indicate that even small changes in maximum tumor diameter within the first week already convey prognostic information.

Early regression of venous phase washout was associated with prolonged PFS in univariate analyses but lost statistical significance in adjusted models. This suggests that washout regression reflects treatment-related vascular change but provides less independent prognostic information than APHE regression in the present cohort. Under LI-RADS TR v2018, LR-TR Viable was assigned when nodular, mass-like, or thick irregular tissue within or along the treated lesion showed APHE, washout appearance, or enhancement similar to pretreatment.(90) Enhancing capsule, although a major feature in the diagnostic LI-RADS algorithm for untreated observations, was not an independent viability criterion in LI-RADS TR v2018. The 2024 CT/MRI nonradiation treatment response algorithm subsequently simplified viability assessment to mass-like enhancement of any degree in any phase.(91) These developments emphasize enhancement morphology rather than a specific contrast phase and are consistent with the dominant prognostic role of APHE regression observed in this study.

Capsule enhancement regression, although frequently observed, did not correlate significantly with PFS, consistent with previous reports.(37)

To integrate the additive prognostic information of individual features, we proposed the Cumulative Regression Score. This simple, visually assessable metric showed a clear stepwise relationship with PFS: each additional regressed feature (APHE, washout, capsule) reduced progression risk by 26% (HR = 0.74, $p = 0.026$). The CRS therefore offers a pragmatic framework for early imaging-based stratification by capturing multiple dimensions of morphologic regression.

Furthermore, we developed the CT-based early response model – a multivariable tool incorporating only two imaging features: APHE regression and early tumor shrinkage. Despite its simplicity, CERM outperformed conventional classification systems such as mRECIST and LI-RADS TR, achieving a higher concordance index and more stable Kaplan-Meier curve separation. This underlines its clinical potential as an early,

individualized risk stratification tool, particularly since it does not require laboratory data – unlike scores such as the Assessment for Retreatment with Transarterial Chemoembolisation (ART) or the Alpha-fetoprotein, Barcelona Clinic Liver Cancer, Child-Pugh, and Response (ABCR) score.(92–94)

Our findings challenge the prevailing notion that early post-embolization imaging is unreliable or uninformative. On the contrary, early morphologic regression patterns convey meaningful prognostic information and can be integrated into structured scoring systems. In particular, enhancement loss rather than size reduction emerged as the dominant driver of early outcome prediction, reflecting the biological target of embolization – tumor devascularization. While enhancement-based criteria such as mRECIST and EASL are typically applied at later timepoints, our results extend their conceptual foundation to the early post-treatment window and support a response-adaptive therapeutic approach.

In conclusion, early imaging markers – particularly APHE regression and tumor shrinkage – are associated with outcome after DEB-TACE. The CRS and CERM provide interpretable tools for early risk stratification and may facilitate individualized, response-adapted treatment strategies.

4.2 Interpretation of Morphologic Regression Patterns

The observed prognostic value of early morphologic regression patterns – particularly APHE and, to a lesser extent, washout – likely reflects fundamental biological changes in tumor perfusion and viability induced by successful DEB-TACE. APHE is a well-established surrogate for viable HCC, indicating the presence of unregulated arterial neovascularization within the tumor.(95,96) Effective DEB-TACE disrupts the pathological arterial supply, leading to ischemia, subsequent devascularization, and ultimately tumor necrosis. Mechanistically, APHE regression likely reflects endothelial damage and microvascular collapse induced by embolic ischemia – changes that precede any measurable reduction in tumor size.(97) The prognostic relevance of APHE regression is supported by histopathological correlation and has been emphasized across multiple studies.(56,98,99)

In contrast, venous phase washout reflects delayed contrast clearance relative to surrounding liver parenchyma and is influenced by several factors including parenchymal perfusion, lesion size and imaging timing.(100–104) Capsule enhancement, though present in some cases before treatment, was inconsistently visualized post-TACE, and its regression did not correlate with outcome in our cohort. This is in line with prior findings suggesting that peripheral enhancement may reflect reactive fibrosis or inflammatory processes rather than viable tumor.(56,105–107) Tumor shrinkage, although often subtle within the first post-treatment week, was an independent predictor of improved PFS in our study. This finding suggests that early reduction in maximum tumor diameter may indicate efficient induction of necrosis and loss of cellular integrity, though several groups have emphasized that size-based metrics like RECIST may underestimate early treatment response compared to enhancement-based markers.(108)

Importantly, the morphologic appearance of the tumor also reflects its underlying biology. In prior literature, tumors with infiltrative margins and irregular arterial enhancement patterns were more likely to exhibit poor early regression and inferior prognosis. Histologically, such patterns are often associated with microvascular invasion or dedifferentiation – factors known to confer resistance to embolization.(36,109) This biological interpretation is further supported by molecular insights: incomplete embolization or treatment-resistant tumors may induce hypoxia-driven signaling cascades involving VEGF and HIF-1 α , promoting neoangiogenesis, immune evasion, and ultimately progression.(110,111) The presence of persistent APHE despite technically successful DEB-TACE may thus not only reflect residual perfusion but also deeper tumor-intrinsic resistance mechanisms. Kim et al. confirmed that imaging patterns consistent with incomplete devascularization were linked to gene expression profiles associated with hypoxia and angiogenesis, lending further support to this hypothesis.(112) Consistent with this, tumors with an expansive, encapsulated nodular phenotype achieved significantly higher rates of complete necrosis after TACE, whereas infiltrative or multinodular growth types showed poor response.(113)

Taken together, early morphologic changes represent not merely radiologic epiphenomena but meaningful indicators of tumor biology and therapeutic vulnerability. Structured interpretation of these features on early imaging may thus serve as a gateway to individualized, biology-informed treatment decisions.

4.3 Methodological Considerations and Imaging Standardization in Early Post-TACE Assessment

The clinical integration of early post-TACE imaging requires methodological robustness and reproducibility across imaging platforms. Beyond biological interpretability, reliable early response assessment depends on standardized acquisition, consistent interpretation, and modality-specific strengths and limitations.

4.3.1 Comparison with Magnetic Resonance Imaging

Magnetic resonance imaging, particularly with hepatobiliary contrast agents like Gd-EOB-DTPA, provides superior soft tissue contrast and higher sensitivity for detecting viable tumor foci compared to CT. Several studies have demonstrated that MRI more reliably detects residual tumor perfusion than contrast-enhanced CT, especially in the presence of Lipiodol artifacts after cTACE.(114,115) Enhancement-based features such as APHE perform robustly on both CT and MRI, although diagnostic performance and inter-reader agreement may vary depending on acquisition parameters and lesion characteristics.(62,63)

The 2024 update in the LI-RADS Treatment Response Algorithm further expands MRI-based assessment by incorporating ancillary features such as diffusion restriction and T2 hyperintensity, particularly in equivocal cases.(116) However, temporal analyses indicate that enhancement loss occurs earlier and more consistently than diffusion changes, supporting vascular regression as the most stable early imaging biomarker.(76)

Despite some advantages, MRI protocols are time-consuming, less widely available, and prone to inter-institutional variability. Importantly, comparative analyses have shown that the overall diagnostic performance of LI-RADS TR categories is comparable between MRI and CT, supporting the use of enhancement-based CT as a pragmatic alternative for early response assessment.(114)

4.3.2 Timing, Acquisition Parameters, and Technical Consistency

Standardization of CT acquisition parameters is critical for reliable early response assessment. Accurate detection of APHE and washout requires precise arterial and portal venous phase timing, thin slice reconstruction, and avoidance of motion artifacts. Even minor deviations in scan timing can significantly impact lesion conspicuity and reader confidence.(64,86) In our own cohort, all post-TACE scans were acquired within 7 days using a standardized multi-phase protocol, allowing for consistent evaluation across patients and treatment cycles.

The type of embolization technique also influences post-treatment imaging. While DEB-TACE tends to induce more homogeneous ischemia, cTACE results in intratumoral lipiodol deposition, potentially masking residual enhancement. This distinction has methodological implications for both visual and quantitative image analysis.(117,118)

4.3.3 Reader Consistency and Reproducibility

Reliable interpretation of regression patterns requires consistent training and inter-reader agreement. Previous validation studies of LI-RADS TR criteria have shown higher agreement for APHE than for additional features such as washout or enhancement similar to pretreatment.(50,63) The use of structured lexicons and standardized interpretation frameworks may therefore improve reproducibility, particularly in longitudinal assessment and multi-center studies.

4.4 Prognostic Modeling and Risk Stratification

4.4.1 Need for Improved Prognostic Tools after TACE

Reliable early prediction of post-TACE outcomes remains challenging. Established response criteria such as mRECIST and LI-RADS TR provide standardized frameworks for treatment assessment but have notable limitations, particularly when applied within the first post-treatment week. mRECIST quantifies viable tumor by measuring the diameters of arterially enhancing tumor components; however, very early treatment effects may manifest primarily as changes in enhancement morphology or intensity that

do not translate into a measurable reduction in enhancing tumor diameter.

Consequently, mRECIST may not fully capture the spectrum of early morphologic response.

LI-RADS TR, while offering a structured qualitative framework, is limited by its categorical structure, and the LR-TR Equivocal category may not provide sufficiently decisive information for clinical management. Previous studies have reported inconsistent prognostic separation between LR-TR Viable and LR-TR Nonviable observations, while the LR-TR Equivocal category showed independent prognostic relevance in some cohorts. In the present cohort, no observations were classified as LR-TR Equivocal. Among the remaining categories, patients with LR-TR Nonviable observations had longer PFS than those with LR-TR Viable observations. Thus, LI-RADS TR provided prognostic information in our study, but its categorical structure still limits the granularity of patient-level risk stratification.

Furthermore, the individual morphologic features did not contribute equally to outcome prediction. Whereas APHE regression emerged as the most informative early imaging feature, capsule enhancement regression was not associated with PFS. Taken together, these findings support the development of a transparent, interpretable, and CT-based model that integrates the most informative early imaging features and provides individualized risk estimates after TACE.

4.4.2 Performance and Interpretation of CERM

The CT-based early response model was designed to provide individualized post-TACE prognostication using APHE regression and continuous tumor shrinkage, both assessable on routine contrast-enhanced CT within the first week. In our cohort, CERM achieved the highest predictive performance among the evaluated parsimonious imaging-only approaches, outperforming individual markers and established response classifications.

CERM achieved a Harrell's C-index of 0.65 with favorable calibration at 180 days (slope: 1.01), and robust internal validity with minimal optimism on bootstrap validation (corrected C = 0.639). Risk-group separation was further supported by a substantial difference in restricted mean survival time (RMST: 145.5 vs. 99.9 days). Although the Cumulative Regression Score was prognostically informative, its

discrimination and calibration were inferior to CERM, supporting the advantage of weighted multivariable modeling over simple summation of regression features. Importantly, CERM offers a pragmatic alternative to more complex or less accessible models. Unlike the ABCR score, which incorporates laboratory markers such as AFP and Child-Pugh class, or the Hepatoma Arterial-embolization Prognostic (HAP) score, CERM is entirely imaging-based and requires no clinical or biochemical input.^(94,119) This enhances its usability in real-world practice, especially when laboratory data are missing, delayed, or confounded by extrahepatic disease. While mRECIST and LI-RADS TR retained independent prognostic relevance in our cohort, their categorical structure limits resolution of early biological heterogeneity. Patients assigned to identical response categories may differ substantially in early morphologic regression, vascular changes, and subsequent outcomes. In contrast, CERM translates early imaging features into a continuous, individualized risk estimate, enabling refined risk stratification even within partial response or equivocal imaging categories.

4.4.3 Risk Stratification and Individual Prediction

One of the key strengths of CERM is its ability to generate continuous, patient-specific risk estimates from early CT features alone and stratify patients into distinct risk groups. Using a simple linear predictor based on APHE regression and tumor shrinkage, individual log-risk scores and time-specific progression risks (e.g., at 90 or 180 days) can be calculated. To facilitate clinical use, we developed a formula and a lookup table that translate model output into illustrative individualized risk estimates.

In our dataset, stratifying patients by the median relative risk score $\exp(LP)$ of 0.781 yielded significant separation of survival curves ($p = 0.008$), with RMST difference increasing from 15.8 days at 90 days to 45.6 days at 180 days. The predictiveness curve demonstrated increasing model-derived risk in the upper risk percentiles, where the probability of early progression increased more steeply.

While full clinical integration and therapeutic consequences are addressed in the following chapter, the current findings underscore the potential of CERM as an early decision-support tool. Unlike categorical criteria such as mRECIST or LI-RADS TR, CERM enables a continuous, nuanced estimation of progression risk and may better

accommodate the biological heterogeneity observed within seemingly uniform response categories such as PR or “viable.”

4.5 Clinical Utility and Decision-Making Implications

The ability to derive individualized risk estimates within the first week after TACE offers tangible clinical value – particularly in a therapeutic context that is increasingly dynamic, response-adapted, and biology-driven. Early CT-based models such as CERM enable proactive decisions at a clinically relevant time point, creating opportunities for personalized management based on early imaging biomarkers.

The CRS, while simple and intuitive, provides a pragmatic overview of early morphologic changes and may be especially useful in multidisciplinary settings where a rapid, visual summary is needed. It stratifies patients based on the number of regressed features and can highlight those with minimal response who may warrant closer attention. However, CRS offers limited resolution for patient-level prediction. In contrast, CERM enables a continuous, individualized risk estimate based on the two most prognostically informative features. While both tools are complementary, CRS may serve as an initial screening aid, and CERM as a more granular model for risk-adapted planning and documentation.

Several potential clinical scenarios emerge from this early risk stratification. Low-risk classification could support standard surveillance, whereas high-risk classification could prompt closer imaging follow-up and earlier multidisciplinary reassessment. Response-adapted treatment strategies are increasingly endorsed by clinical guidelines. Recent international guidelines recommend an early transition to systemic therapy in cases of TACE refractoriness.(2,18,120) In this context, recent randomized trials have demonstrated that the addition of systemic therapy to TACE improves clinical outcomes compared with TACE monotherapy. The TACTICS trial showed a significant prolongation of PFS in intermediate-stage HCC patients treated with TACE plus sorafenib.(121) Similarly, Fan et al. reported superior overall survival and PFS in patients with early-stage recurrent HCC and microvascular invasion when treated with a combination of TACE and sorafenib.(122)

As mentioned, morphologic tumor subtypes (e.g., nodular vs. infiltrative) strongly influence response and prognosis. Early non-response in infiltrative HCC patterns may

reflect deeper biological resistance, such as microvascular invasion or hypoxia-driven angiogenic signaling.(123) In these patients, repeated embolization may be futile, and earlier transition to systemic options – potentially including clinical trial enrollment – should be considered. Notably, early combination therapy (e.g., DEB-TACE plus Lenvatinib) may outperform monotherapy in patients otherwise deemed unsuitable for systemic treatment.(124)

The integration of CERM into multidisciplinary tumor boards could provide a transparent and interpretable framework to guide complex decisions. Its reliance on two imaging features facilitates interpretation across radiology, oncology, and hepatology, even in the absence of laboratory data. Beyond informing treatment selection, early risk modeling can assist in communication, documentation, and coordination of care. In practice, integrating CERM into structured radiology reports or tumor board templates may support longitudinal decision-making and facilitate harmonized follow-up planning.

In sum, CERM operationalizes the principles of response-adapted therapy advocated in modern HCC guidelines and bridges a critical gap in post-TACE decision-making. Its preliminary risk stratification may help define hypotheses for future studies evaluating surveillance intensity and timely therapeutic reassessment.

4.6 Limitations and Sources of Bias

Despite its strengths, this study has several limitations that should be acknowledged. First, the retrospective single-center design entails a risk of selection bias and limits the external validity of the results. Patient selection, treatment decisions, and follow-up procedures were determined by local clinical practice and may differ from those at other institutions. At the same time, all patients were treated and evaluated within a uniform institutional framework, with consistent interventional techniques and imaging protocols. This homogeneity reduced procedural variability and strengthened the internal comparability of the study cohort.

Second, CERM was developed and internally validated in the same cohort. Bootstrap validation indicated only limited optimism, but it cannot substitute for evaluation in an independent dataset, and the transportability of the model to other patient populations, CT systems, contrast protocols, and institutional workflows remains unknown. The

present internal validation therefore provides a methodological basis for subsequent external validation across independent centers, scanner vendors, and acquisition protocols.

Third, the principal imaging features, including APHE regression, washout regression, and capsule enhancement regression, were assessed qualitatively. Regression was defined as complete disappearance of a feature rather than as a gradual or quantitative change, which simplified classification but may have reduced sensitivity to more subtle treatment effects. No volumetric, perfusion-based, or radiomic measurements were included, and interobserver agreement was not quantified separately. However, the imaging features were assessed using prespecified definitions, evaluated independently by two board-certified radiologists who were blinded to patient outcomes, and resolved by consensus in cases of disagreement. Future multi-reader studies and quantitative image-analysis approaches should determine the reproducibility and incremental value of these qualitative definitions.

Fourth, tumor shrinkage was defined as any decrease in maximum unidimensional diameter. Given the 2-mm reconstructed slice thickness and manual measurements, small differences may partly reflect measurement variability rather than true biological response. However, the use of a simple routinely available diameter measurement enhances practical feasibility and provides a pragmatic basis for future studies applying prespecified minimum-change thresholds and formal reproducibility analyses.

Fifth, the primary endpoint was radiological progression-free survival, defined as the time to the first radiologically documented progression. Although this represents a clinically relevant time-to-event outcome in a predominantly nonsurgical population, progression was determined radiologically and treatment response was not confirmed histopathologically. The biological correlates of early enhancement regression, such as tumor necrosis, endothelial injury, or microvascular collapse, could therefore not be directly verified. In addition, APHE and washout may contribute both to the imaging predictors and to the subsequent radiological assessment of progression, creating a potential risk of incorporation bias. Nevertheless, the time-to-event analysis of radiologically documented progression provided a clinically interpretable longitudinal outcome measure. Future studies should complement this endpoint with overall survival, independent clinical outcomes, functional imaging, or pathological validation where available.

Finally, the model depends on the technical quality and timing of multiphasic contrast-enhanced CT. The institutional protocol did not include a delayed phase; consequently, washout and capsule enhancement were assessed exclusively on portal venous images. This may have reduced sensitivity for subtle manifestations of these features, particularly in small lesions, and may have weakened their observed prognostic performance. Minor variations in contrast timing, patient motion, or arterial phase acquisition could also have influenced enhancement assessment. However, all examinations were performed on a single scanner using a standardized acquisition and reconstruction protocol, which minimized technical heterogeneity within the present cohort. Evaluation on other scanner platforms using harmonized multiphasic protocols represents an important next step.

Taken together, these limitations require cautious interpretation of the reported effect estimates and model performance. The results should therefore be regarded as internally validated, hypothesis-generating evidence rather than as proof of immediate clinical applicability. Nevertheless, the use of routinely available CT features, prespecified image definitions, blinded assessment, and a uniform acquisition protocol provides a coherent foundation for independent prospective validation and further methodological refinement.

4.7 Future Directions and Perspectives

The promising results of this study highlight the potential of early imaging biomarkers for individualized treatment planning after TACE. However, to realize the full clinical utility of the CT-based early response model, several future directions should be pursued, spanning methodological, biological, and implementation-related dimensions. First, external validation is essential. To ensure transportability and guard against center-specific biases, prospective validation in multicenter settings is needed. Such efforts should standardize post-TACE CT protocols and assess reproducibility across platforms and clinical workflows.

Second, the binary alternative to CERM – Model 6b, which combines APHE regression with binary tumor shrinkage (Appendix, Tables A3-A4) – warrants further evaluation. Its dichotomous structure may simplify clinical implementation and facilitate rule-based classification without requiring the exact magnitude of tumor shrinkage to be entered as

a continuous variable. Direct comparison with CERM in independent cohorts should quantify the trade-off between operational simplicity and predictive performance. Third, integration with clinical and biological markers should be explored. While CERM is intentionally lab-independent, combining it with dynamic biomarkers such as AFP kinetics, ALBI changes, or inflammatory scores may enhance stratification, especially in borderline cases. A hybrid model incorporating CERM with other inputs could define new phenotypes of treatment response.

Fourth, radiomics and artificial intelligence offer considerable expansion potential. Quantitative texture and spatial metrics may detect sub-visual morphologic changes, enhancing early prediction. Microvascular damage and subtle heterogeneity post-TACE may be underestimated by visual analysis alone. Semi-automated segmentation and APHE intensity scoring – using volumetric maps, histogram analysis, or subtraction techniques – could improve the objectivity of response assessment and enhance model input quality. However, recent findings suggest that advanced CT techniques do not automatically improve diagnostic accuracy after TACE.

Fifth, tool implementation must follow principles of usability and workflow integration. CERM could be technically implemented using routinely acquired multiphasic CT data after successful external validation. The next step is operational translation: web-based calculators, PACS-integrated scripts, or structured reporting templates could deliver patient-specific risk estimates directly into clinical workflows. Embedding CERM scores into multidisciplinary tumor board reports could support early, consistent decision-making across specialties.

Sixth, the cumulative regression score deserves additional validation. While simpler than CERM, CRS may function as a triage tool – quickly flagging non-responders in busy clinical settings. Its role in risk pre-screening, education, or automated extraction from structured reports should be explored further. Hybrid workflows using CRS as a filter and CERM for detailed modeling may be especially efficient in high-throughput environments.

Lastly, prospective studies should move beyond survival prediction to adaptive therapy modeling. Response heterogeneity after TACE is influenced by vascular remodeling, angiogenic signaling, and immune microenvironment – all of which could serve as future modifiers of risk prediction. Research should evaluate how early morphologic signatures interact with systemic therapies, particularly in sequential or combination

regimens. Early stratification could help identify candidates for intensified treatment—before morphologic progression manifests.

In summary, the next generation of prognostic modeling in HCC will be defined by prospective validation, digital integration, and biological fusion. CERM provides an interpretable, imaging-based foundation. By embedding it into multidisciplinary workflows, combining it with quantitative tools and biomarkers, and validating it across institutions, we can move closer to truly individualized, early-adaptive treatment strategies in HCC.

4.8 Conclusion

Contrast-enhanced CT within seven days after DEB-TACE yielded clinically relevant prognostic information well before conventional follow-up imaging. APHE regression emerged as the most robust early imaging marker of prolonged PFS, while early tumor shrinkage provided complementary prognostic value. CERM combined both features in a parsimonious imaging-only model and showed moderate discrimination, limited bootstrap optimism, and significant risk-group separation in the development cohort. These findings support early CT as a practical and promising basis for further evaluation of response-adapted surveillance and treatment planning after DEB-TACE.

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6 Appendix

Table A1. Results of univariate Cox regression analyses assessing the association between clinical, imaging, and laboratory variables and PFS. Only variables with statistically significant associations ($p < 0.05$) are shown.

Variable	HR	95% CI	p-value
Size after TACE	1.17	1.10–1.25	<0.001
Size before TACE	1.15	1.07–1.24	<0.001
Tumor Shrinkage (binary)	0.50	0.3–0.83	0.007
Tumor Shrinkage (continuous)	0.73	0.54–0.99	0.040
Extrahepatic Metastasis	4.99	2.27–10.96	<0.001
Macroscopic Vascular Involvement	7.28	2.09–25.29	0.002
Washout after TACE	2.45	1.37–4.4	0.003
Regression of Washout	0.41	0.22–0.76	0.005
APHE after TACE	1.90	1.14–3.19	0.015
Regression of APHE	0.49	0.28–0.83	0.008
mRECIST after TACE (CR vs. PR)	0.49	0.29–0.83	0.009
LI-RADS TR (non-viable vs. viable)	0.53	0.32–0.9	0.026
CRS	0.74	0.57–0.97	0.026
CRS = 1 vs. 0	0.40	0.20–0.83	0.014
CRS = 2 vs. 0	0.42	0.22–0.82	0.010
CRS = 3 vs. 0	0.36	0.16–0.81	0.014

Table A2. Results of univariate Cox regression analyses for non-significant predictors.

Variable	HR	95% CI	p-value
logAFP	1.10	0.98–1.23	0.116
Child-Pugh Class	0.72	0.48–1.09	0.123
ALBI-Score	0.98	0.60–1.63	0.953
ALBI Grade	1.21	0.76–1.92	0.418
Bilirubin	0.92	0.65–1.32	0.665
Albumin	0.98	0.58–1.66	0.945
Psoas-Muscle-Index	0.92	0.79–1.05	0.221
APHE before TACE	0.88	0.4–1.94	0.754
Washout before TACE	1.39	0.8–2.42	0.238
Capsule Enhancement before TACE	1.00	0.61–1.65	0.999
Capsule Enhancement after TACE	1.90	0.59–6.13	0.282
Regression of Capsule Enhancement	0.49	0.14–1.71	0.263
Milan Criteria	0.78	0.48–1.26	0.304

Table A3. Overview of all multivariate Cox regression models developed to evaluate independent predictors of PFS. Models M1–M8 were constructed as exploratory candidate models using variables with significant univariable associations. Models M9–M12 were clinically informed benchmark models that additionally included variables selected on the basis of clinical plausibility despite nonsignificant univariable associations. Model M6a was selected as the CT-based early response model (CERM).

Model ID	Included Variables	Type
M1	APHE Regression, Washout Regression, Tumor Shrinkage (binary)	Exploratory
M2	Size before TACE, Size after TACE, Macroscopic Vascular Involvement	
M3a	CRS, Tumor Shrinkage (continuous)	
M3b	CRS (categorical), Tumor Shrinkage (continuous)	
M4a	mRECIST, Extrahepatic Metastasis	
M4b	mRECIST, Tumor Shrinkage (binary)	
M5a	LI-RADS TR, Extrahepatic Metastasis	
M5b	LI-RADS TR, Tumor Shrinkage (binary)	
M6a	APHE Regression, Tumor Shrinkage (continuous)	Selected Model
M6b	APHE Regression, Tumor Shrinkage (binary)	Exploratory
M7	APHE Regression, Extrahepatic Metastasis	
M8	APHE Regression, Size after TACE	
M9	APHE Regression, logAFP, ALBI Score	
M10	APHE Regression, Tumor Shrinkage (binary), logAFP	Clinically informed benchmark
M11	APHE Regression, logAFP, Extrahepatic Metastasis	
M12	APHE Regression, Washout Regression, Tumor Shrinkage (continuous), logAFP, ALBI Score, Extrahepatic Metastasis	

Table A4. Multivariable Cox regression results for models M1–M12. Shown are hazard ratios (HRs), 95% confidence intervals (CI), p-values, global model p-values, Harrell's C-index, sample size (n), number of events, and variance inflation factor (VIF).

Model	Variable	HR	95% CI	p-value	Global p-value	C-index	n	Events	VIF
M1	APHE regression	0.63	0.14–2.75	0.537	0.014	0.66	55	49	3.61
	Washout regression	0.66	0.15–2.91	0.583					3.75
	Tumor shrinkage (binary)	0.61	0.33–1.13	0.118					1.02
M2	Size before TACE	0.81	0.60–1.10	0.184	0.001	0.63	80	68	47.22
	Size after TACE	1.40	1.03–1.89	0.030					47.39
	Macroscopic vascular involvement	2.10	0.46–9.51	0.336					1.17
M3a	CRS	0.72	0.55–0.93	0.014	0.014	0.63	76	66	1.00
	Tumor shrinkage	0.70	0.50–0.99	0.045					1.00
M3b	CRS 1	0.42	0.20–0.86	0.017	0.026	0.66	76	66	1.58
	CRS 2	0.44	0.23–0.85	0.015					1.62
	CRS 3	0.32	0.14–0.73	0.007					1.38
	Tumor shrinkage	0.72	0.50–1.03	0.071					1.02
M4a	mRECIST	0.53	0.31–0.91	0.022	<0.001	0.64	71	61	1.05
	Extrahepatic metastasis	4.59	1.94–10.86	<0.001					1.05
M4b	mRECIST	0.49	0.29–0.84	0.010	0.002	0.65	71	61	1.00
	Tumor shrinkage (binary)	0.53	0.31–0.91	0.021					1.00
M5a	LI-RADS TR	0.57	0.34–0.96	0.034	<0.001	0.63	76	66	1.03
	Extrahepatic metastasis	4.68	2.10–10.44	<0.001					1.03
M5b	LI-RADS TR	0.54	0.32–0.91	0.021	0.007	0.62	76	66	1.00
	Tumor shrinkage (binary)	0.57	0.34–0.96	0.035					1.00
M6a	APHE regression	0.49	0.29–0.84	0.009	0.012	0.65	71	61	1.01
	Tumor shrinkage	0.76	0.54–1.06	0.107					1.01

Model	Variable	HR	95% CI	p-value	Global p-value	C-index	n	Events	VIF
M6b	APHE regression	0.49	0.29–0.84	0.009	0.002	0.65	71	61	1.00
	Tumor shrinkage (binary)	0.53	0.31–0.91	0.021					1.00
M7	APHE regression	0.53	0.31–0.91	0.022	<0.001	0.64	71	61	1.05
	Extrahepatic metastasis	4.61	1.95–10.89	<0.001					1.05
M8	APHE regression	0.71	0.38–1.32	0.277	0.001	0.64	71	61	1.37
	Size after TACE	1.14	1.05–1.25	0.002					1.37
M9	APHE regression	0.38	0.21–0.69	0.001	0.009	0.65	66	57	1.01
	logAFP	1.16	1.02–1.31	0.025					1.01
	ALBI score	1.01	0.58–1.75	0.970					1.02
M10	APHE regression	0.40	0.22–0.72	0.002	0.001	0.66	66	57	1.01
	Tumor shrinkage (binary)	0.52	0.29–0.92	0.026					1.01
	logAFP	1.16	1.03–1.32	0.014					1.00
M11	APHE regression	0.41	0.22–0.75	0.004	<0.001	0.67	66	57	1.05
	logAFP	1.15	1.02–1.30	0.025					1.01
	Extrahepatic metastasis	4.28	1.78–10.27	0.001					1.06
M12	APHE regression	0.34	0.07–1.57	0.166	0.003	0.69	51	46	4.57
	Washout Regression	0.96	0.21–4.39	0.956					4.74
	Tumor Shrinkage	0.78	0.56–1.10	0.163					1.03
	logAFP	1.16	1.01–1.33	0.040					1.07
	ALBI Score	1.03	0.54–1.96	0.940					1.11
	Extrahepatic Metastasis	3.89	1.46–10.38	0.007					1.15

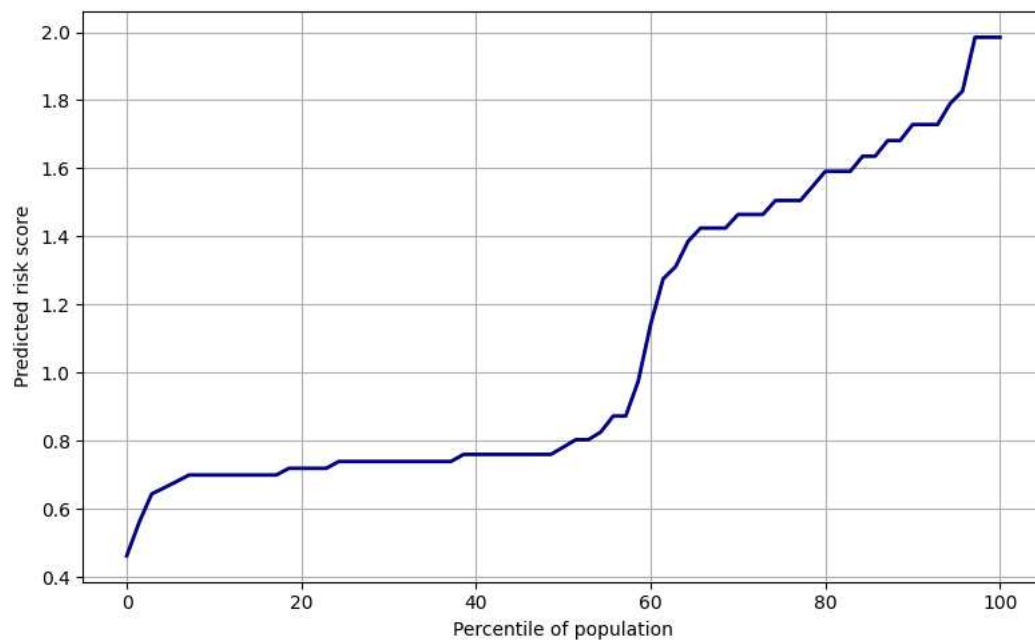


Figure A1. Predictiveness curve for CERM showing the distribution of model-derived relative risk scores across the cohort. Scores increased more steeply above the 60th percentile.

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