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Multiphasic CT Delta Radiomics for Four-Class Prediction of Combined VETC/MVI Phenotypes In Hepatocellular Carcinoma

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ABSTRACT

Purpose: Preoperative phenotyping of vessels that encapsulate tumor clusters (VETC) and microvascular invasion (MVI) is clinically important in hepatocellular carcinoma (HCC) diagnosis and treatment. While most studies rely on MRI, CT-based prediction remains limited despite multiphasic contrast-enhanced CT being widely available. This study aims to develop and evaluate multiphase CT radiomics models for four-class prediction of combined VETC/MVI phenotypes using single-phase (arterial [AP], delayed [DP], portal venous [PVP]) or inter-phase delta features.

Methods: This retrospective study included 366 patients with HCC: VETC-/MVI- (148), VETC+/MVI+ (82), VETC-/MVI+ (61), and VETC+/MVI- (75). Triphasic CT images and tumor masks were resampled and registered. PyRadiomics features were extracted with fixed discretization. Models were trained using single-phase features (AP, DP, PVP) and delta features (AP-DP, AP-PVP, DP-PVP). Feature selection followed a five-step pipeline with six method combinations, comprising SIS, within-category correlation filtering or VIF, relevance confirmation, and embedded selection using RF/ElasticNet/Lasso. Class imbalance was addressed using class-weighted loss. Ten types of classifiers (e.g., SVM, RF, LR, XGBoost) were evaluated using class-wise and macro AUC. The dataset was split into 90% for stratified five-fold cross-validation and 10% for independent testing.

Results: Delta radiomics outperformed single-phase models for the four-class VETC/MVI prediction tasks. The optimal delta radiomics model (DP-PVP; VIF-RF; XGBoost) achieved a final macro-AUC of 0.847, with the strongest class-wise discrimination for MVI+/VETC- (AUC=0.957) and VETC+/MVI+ (AUC=0.905). Among single-phase models, AP showed the highest macro-AUC of 0.764 (Correlation-LASSO; LDA), whereas DP and PVP both achieved macro-AUC of 0.745 (VIF-RF; Random Forest).

Conclusion: Inter-phase delta radiomics improved four-class VETC/MVI classification task performance compared to single-phase features, suggesting that cross-phase image-based biomarkers may capture additional vascular invasion-related information. Class-wise performance showed some heterogeneity, suggesting differentiated separability across phenotypes. Multi-institutional validation and robustness analyses across acquisition settings are warranted to enhance generalizability.

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INTRODUCTION

Hepatocellular carcinoma (HCC) demonstrates substantial biological heterogeneity, which affects prognosis and treatment planning. Two important histopathologic phenotypes, vessels that encapsulate tumor clusters (VETC) and microvascular invasion (MVI), are associated with tumor aggressiveness but are typically confirmed only after surgery. **Figure 1** illustrates these two phenotypes.

Preoperative imaging-based prediction of VETC and MVI may support risk stratification and individualized clinical decision-making. Although MRI-based approaches have been widely investigated, CT-based prediction remains less explored despite the broad availability of multiphasic contrast-enhanced CT in routine HCC evaluation.

Contrast-enhanced CT captures dynamic patterns across arterial, portal venous, and delayed phases, which may potentially reflect tumor vascularity and microenvironmental characteristics. Therefore, this study investigates whether radiomics methods based on triphasic contrast-enhanced CT can predict combined four-class VETC/MVI phenotypes in HCC.

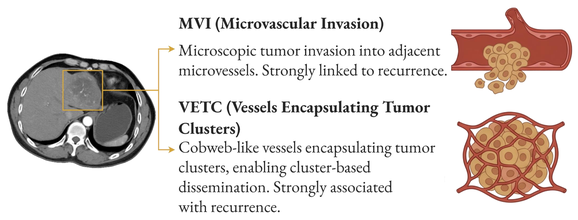

Figure 1. Schematic Diagram of MVI & VETC in Hepatocellular Carcinoma

METHODS AND MATERIALS

This retrospective study included 366 patients with pathologically confirmed HCC, categorized into four VETC/MVI phenotypes: VETC-/MVI- (n = 148), VETC+/MVI+ (n = 82), VETC-/MVI+ (n = 61), and VETC+/MVI- (n = 75). Patient enrollment and cohort construction are summarized in **Figure 2**.

Triphasic contrast-enhanced CT images, including arterial phase (AP), portal venous phase (PVP), and delayed phase (DP), were resampled and registered. Tumor regions were segmented, and radiomics features were extracted using PyRadiomics.

Single-phase features were extracted from AP, PVP, and DP images. Inter-phase delta features were calculated from AP-DP, AP-PVP, and DP-PVP pairs to capture dynamic enhancement-related information. Feature selection and classifier training were performed using machine-learning pipelines.

The dataset was split into 90% training/validation and 10% independent testing. Stratified five-fold cross-validation was performed, and performance was evaluated using one-vs-rest class-wise AUC and macro-average AUC.

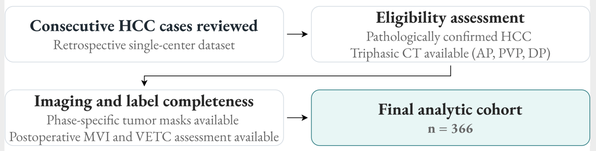

Figure 2. Flowchart of Patient Enrollment and Cohort Construction

RESULTS

Inter-phase delta radiomics models showed overall higher performance than single-phase CT models for four-class VETC/MVI phenotype prediction.

The best-performing model used DP-PVP delta features with VIF-RF feature selection and an XGBoost classifier, achieving a final macro-average AUC of 0.847. This model demonstrated the strongest class-wise discrimination for MVI+/VETC- and VETC+/MVI+, with AUCs of 0.957 and 0.905, respectively.

Among single-phase models, AP achieved the highest macro-average AUC of 0.764 using correlation-LASSO feature selection and LDA classification. DP and PVP each achieved a macro-average AUC of 0.745 using VIF-RF feature selection and Random Forest classification.

Overall, delta feature models, particularly DP-PVP and AP-PVP, provided more favorable discrimination than single-phase models, although performance varied across the four VETC/MVI phenotypes (**Figure 3**). Final one-vs-rest macro-AUC was used to rank feature constructions and classifiers across single-phase and inter-phase delta radiomics models, showing that delta feature sets generally achieved higher macro-average AUCs than individual CT phases (**Figure 4**). ROC analysis further confirmed the added value of delta-based models, suggesting that cross-phase enhancement changes may capture complementary information for differentiating combined VETC/MVI phenotypes.

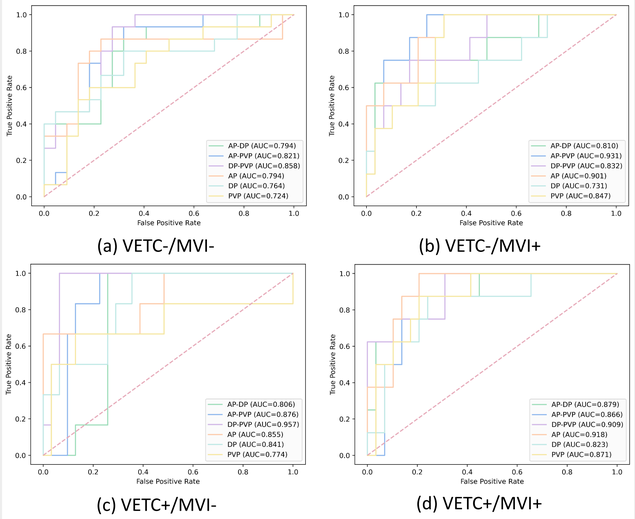

Figure 3. One-vs-Rest ROC Curves for Four-Class VETC/MVI: Single-Phase vs. Inter-Phase Delta Radiomics

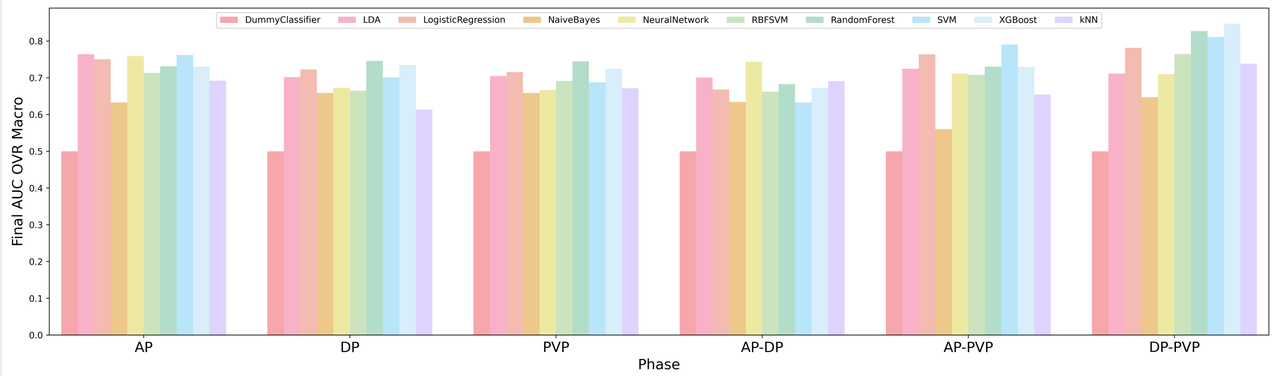

Figure 4. Final One-vs-Rest Macro AUC across Phases, Phase Pairs and Models

DISCUSSION

This study demonstrates that inter-phase delta radiomics provides improved performance over single-phase CT radiomics for four-class VETC/MVI phenotype prediction in HCC. The superior performance of delta features suggests that enhancement changes across CT phases may capture complementary hemodynamic and microenvironment-related information associated with tumor vascular architecture and invasive behavior.

The DP-PVP delta model achieved the highest macro-average AUC, indicating that delayed and portal venous phase differences may provide particularly useful information for distinguishing combined VETC/MVI phenotypes. However, class-wise AUCs varied across phenotypes, suggesting that some VETC/MVI groups may be more radiologically separable than others.

These findings support the potential value of multiphasic CT radiomics as a noninvasive tool for preoperative HCC risk stratification. Future work should include multi-institutional validation, assessment of feature robustness across CT acquisition protocols, and integration with clinical or semantic imaging features to improve generalizability and clinical translation.

CONCLUSIONS

Inter-phase delta radiomics improved four-class VETC/MVI phenotype prediction compared with single-phase CT radiomics in HCC.

The DP-PVP delta model achieved the best overall performance, suggesting that cross-phase enhancement changes may provide useful imaging biomarkers related to tumor vascular invasion and microenvironmental heterogeneity.

Multiphasic CT delta radiomics may support noninvasive preoperative risk stratification, although external validation is needed before clinical translation.

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