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CMIR: A Unified Cross-Modality Framework for Preoperative Accurate Prediction of Microvascular Invasion in Hepatocellular Carcinoma

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Abstract. Microvascular invasion of HCC is an important factor affecting postoperative recurrence and prognosis of patients. Preoperative diagnosis of MVI is greatly significant to improve the prognosis of HCC. Currently, the diagnosis of MVI is mainly based on the histopathological examination after surgery, which is difficult to meet the requirement of preoperative diagnosis. Also, the sensitivity, specificity and accuracy of MVI diagnosis based on a single imaging feature are low. In this paper, a robust, high-precision cross-modality unified framework for clinical diagnosis is proposed for the prediction of microvascular invasion of hepatocellular carcinoma. It can effectively extract, fuse and locate multi-phase MR Images and clinical data, enrich the semantic context, and comprehensively improve the prediction indicators in different hospitals. The state-of-the-art performance of the approach was validated on a dataset of HCC patients with confirmed pathological types. Moreover, CMIR provides a possible solution for related multimodality tasks in the medical field.

Keywords. Microvascular invasion, deep learning, accurate prediction

1. Introduction

Hepatocellular carcinoma (HCC) is a global health challenge, one of the most common and most lethal malignant tumors, with a growing burden worldwide [1,2]. World Health Organization estimates that more than 1 million people will die from HCC in 2030 [3]. Surgical resection and liver transplantation are potential treatments for HCC [4]. However, tumor recurrence occurs in 70% of cases after hepatectomy and in 25% of cases after liver transplantation, and the 5-year overall survival rate is approximately

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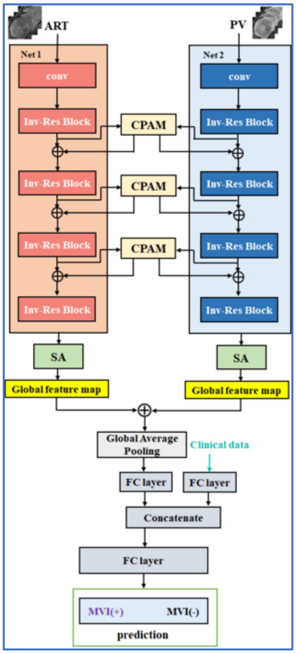
10%-20% [5]. Microvascular invasion (MVI), defined as the presence of tumor emboli in the portal vein, capsule vessels, or vascular spaces lined with endothelial cells, has been shown to be an independent risk factor associated with early recurrence and poor survival after resection and transplantation. MVI can only be confirmed by histopathological examination of postoperative surgical specimens. Early prediction of MVI has important guiding significance for preoperative selection of liver transplantation recipients, formulation of surgical plan (anatomic hepatectomy or non-anatomic hepatectomy), postoperative adjuvant therapy and prognosis.

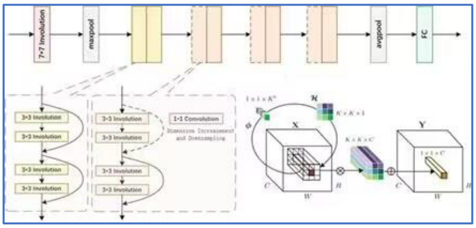
Preoperative prediction of MVI mainly relies on imaging examinations, macroscopic tumor features, and serum markers [6]. These methods mainly rely on the subjective judgment of doctors, lack objective quantitative indicators, and have insufficient sensitivity, specificity, and accuracy in diagnosing MVI based on a single imaging feature, and cannot accurately judge the occurrence of MVI in patients. This paper mainly focuses on the problem of accurate prediction of MVI of HCC using multi-phase MR images and clinical data, and proposes a unified cross-modality prediction framework, which is robustly verified in six hospitals. Multi-parameter MRI showed uniform or heterogeneous enhancement of liver tumors in the arterial (ART) phase, and the enhancement of liver tumors in the portal venous (PV) phase was lower than that of the liver parenchyma. Each phase contains some different important information. Therefore, it is important to obtain rich contextual information and select complementary sets. To achieve this, we propose a unified model for accurate prediction of MVI in HCC: a cross-modality involution residual network, which deeply mines and fuses the semantic information of MRI multi-phase images and clinical data to effectively improve the survival rate of patients, improve clinical decision-making, and solve the problems of the existing model with high specificity but low sensitivity and insufficient predictive ability, which cannot be applied in clinical practice.

2. Methods

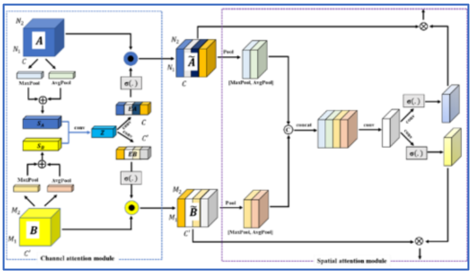
As shown in Figure 1, our proposed method retains essential details of each phase while selecting fusing features from multimodality data, resulting in effectively combining the informative contextual information of multi-phase MR images and clinical data. The main contributions of the proposed method are: (1) We present a unified cross-modality framework for preoperative accurate prediction of MVI in HCC named cross-modality involution ResNet (CMIR) to extract important and complementary features, enhance key details, and fuse them efficiently. This method can significantly emphasize the complementary multiphase contextual information for the prediction. (2) We design a spatially specific backbone network and multi-phase fusion modules called involution residual network (Inv-ResNet) and cross-phase attention module (CPAM). Inv-ResNet combines ResNet blocks (residual learning) and involution operators to extract discriminative features within each phase, and CPAM is used to selectively complete cross-phase enhanced information exchange and fusion at each layer. (3) We propose a positioning module with global-squeeze and spatial attention to intelligently locate the MVI where is most likely to occur in HCC, which is superior to the existing methods in terms of accuracy, AUC, sensitivity and specificity.



(a) CMIR: a unified cross-modality framework



(b) Inv-ResNet schematic diagram and involution operator.



(c) Cross-phase attention module (CPAM)

Figure 1. The framework and main modules of the proposed method.

2.1. Inv-ResNet

Unlike Convolution, involution uses a shared kernel in channel dimension and adopts space-specific kernel $\mathcal{H} \in \mathbb{R}^{H \times W \times K \times G \times G}$ for more flexible modeling in space dimension. The abstract representation of Involution operator is shown in Figure 1(b).

$$Y_{i,j,k} = \sum_{(u,v)\in\Delta k} \mathcal{H}_{i,j,u+[K/2],v+[K/2],[KG/C]} X_{i+u,j+v,k}, \qquad (1.)$$

2.2. Cross-Phase Attention Module (CPAM)

Inspired by the use of the Squeeze and excitation (SE) module for single-mode convolutional neural networks, we propose a CPAM module to recalibrate and emphasize key meaningful information features across spatial and channel dimensions of different CNN streams, enhancing and exchanging important feature information, before fusing the feature maps of each MR Phase. CPAM is a lightweight general-purpose module that can be seamlessly integrated into any CNN architecture with negligible overhead and can be trained end-to-end together with the base CNN. Figure 1(c) explains this process.

2.3. Feature Localization Module

After fusing MR multi-phase features, we propose a spatial localization module for the fused high-level features: Spatial Attention (SA). Then clinical data were added and fused again to predict the MVI.

2.4. Experimental Setup

We use five different hospitals in our experiment, they all collected from September 2012 to September 2020, divided according to the ratio of 8:2.

Table 1. Multi-phase MRI dataset.

	Training set	**Internal validation set**	**External validation set**			
Hospital name	Zhejiang Province Run Run Shaw Hospital (RRSH)	Zhejiang Province Run Run Shaw Hospital (RRSH)	The First Provincial Wenzhou Hospital of Zhejiang (FPWH)	Li Huili Hospital (LHH)	Zhejiang Taizhou Hospital (ZTH)	Zhejiang First Hospital (ZFH)
Number of cases	406		130	102	185	79
MVI (+)	124	31	42	61	40	20
MVI (-)	201	50	88	41	145	59
Positive and negative ratio	1:1.62	1:1.61	1:2.1	1:0.67	1:3.625	1:1.97

3. Results

We quantitatively compare the proposed model with existing deep learning methods. As shown in Table 2, the results show that the proposed method achieves the state-of-the-art in all three metrics (accuracy, sensitivity, specificity).

Table 2. The results of the experimental comparison in five hospitals.

Method	**Training set**	**Internal validation set**	**External validation set**			
	RRSH	**RRSH**	**FPWH**	**LHH**	**ZTH**	**ZFH**
3D CNN-LSTM	0.874 (0.796, 0.803)	0.760 (0.740, 0.786)	0.702 (0.691, 0.711)	0.727 (0.700, 0.714)	0.673 (0.658, 0.696)	0.694 (0.684, 0.702)
DLC	0.880 (0.801, 0.798)	0.773 (0.752, 0.790)	0.700 (0.701, 0.706)	0.741 (0.724, 0.756)	0.713 (0.700, 0.708)	0.696 (0.692, 0.694)
IVIM	0.885 (0.812, 0.845)	0.782 (0.760, 0.798)	0.728 (0.720, 0.724)	0.755 (0.730, 0.759)	0.700 (0.708, 0.713)	0.721 (0.721, 0.752)
MVI-Mind	0.887 (0.824, 0.821)	0.789 (0.760, 0.800)	0.731 (0.734, 0.755)	0.756 (0.728, 0.764)	0.712 (0.723, 0.698)	0.720 (0.716, 0.768)
TED	0.903 (0.858, 0.819)	0.796 (0.787, 0.810)	0.735 (0.745, 0.769)	0.759 (0.741, 0.766)	0.715 (0.728, 0.717)	0.742 (0.754, 0.787)
Proposed	0.926 (0.892, 0.834)	0.845 (0.814, 0.803)	0.794 (0.791, 0.786)	0.819 (0.806, 0.812)	0.767 (0.782, 0.778)	0.801 (0.816, 0.800)

4. Discussion

We performed internal and external validation at the five hospitals listed in Table 1 using five-fold cross-validation. It can be observed that although our proposed algorithm has achieved the state-of-the-art performance, due to the different MR scanning machines used in different hospitals and the difference in the proportion of positive and negative samples, the prediction accuracy in different hospitals is not consistent. Overall, the proposed architecture performs optimally in several hospitals.

5. Conclusions

This paper proposes a robust, high-precision cross-modal unified framework named CMIR based on multi-phase MR images and clinical data, and applies it to the accurate prediction of microvascular invasion in HCC. Three important feature extraction, fusion and localization modules Inv-ResNet, CPAM and SA are proposed, they enrich the semantic information across modalities and achieve the state-of-the-art performance on different hospitals.

Acknowledgements

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References

[1] Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J, Finn RS. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021 Jan;7(1):6, doi: 10.1038/s41572-020-00240-3.
[2] Wang W, Guo Y, Zhong J, Wang Q, Wang X, Wei H, Li J, Xiu P. The clinical significance of microvascular invasion in the surgical planning and postoperative sequential treatment in hepatocellular carcinoma. Sci Rep. 2021 Jan;11(1):2415, doi: 10.1038/s41598-021-82058-x.
[3] Samant H, Amiri HS, Zibari GB. Addressing the worldwide hepatocellular carcinoma: epidemiology, prevention and management. J Gastrointest Oncol. 2021 Jul;12(Suppl 2):S361-73, doi: 10.21037/jgo.2020.02.08.
[4] Mak LY, Cruz-Ramón V, Chinchilla-López P, Torres HA, LoConte NK, Rice JP, Foxhall LE, Sturgis EM, Merrill JK, Bailey HH, Méndez-Sánchez N, Yuen MF, Hwang JP. Global epidemiology, prevention, and management of hepatocellular carcinoma. Am Soc Clin Oncol Educ Book. 2018 May;38:262-79, doi: 10.1200/EDBK_200939.
[5] Reveron-Thornton RF, Teng MLP, Lee EY, Tran A, Vajanaphanich S, Tan EX, Nerurkar SN, Ng RX, Teh R, Tripathy DP, Ito T, Tanaka T, Miyake N, Zou B, Wong C, Toyoda H, Esquivel CO, Bonham CA, Nguyen MH, Huang DQ. Global and regional long-term survival following resection for HCC in the recent decade: a meta-analysis of 110 studies. Hepatol Commun. 2022 Jul;6(7):1813-26, doi: 10.1002/hep4.1923.
[6] Zhang X, Ruan S, Xiao W, Shao J, Tian W, Liu W, Zhang Z, Wan D, Huang J, Huang Q, Yang Y, Yang H, Ding Y, Liang W, Bai X, Liang T. Contrast-enhanced CT radiomics for preoperative evaluation of microvascular invasion in hepatocellular carcinoma: a two-center study. Clin Transl Med. 2020 Jun;10(2):e111, doi: 10.1002/ctm2.111.