综 述

影像组学预测肝细胞癌微血管侵犯的研究现状*

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【摘要】肝细胞癌(HCC)是目前对人类健康造成巨大威胁的常见恶性肿瘤之一，由于其发病率、死亡率都很高以及预后不理想，对于肝细胞癌的治疗一直都是我们需要攻克的难题。微血管侵犯(MVI)已经被多项研究证实是肝细胞癌术后复发以及预后不良的重要原因。然而，MVI的诊断主要是在术后通过肝细胞癌的病理学检查来确诊。如果能在术前对MVI进行一定的预测，将会对指导个体化治疗方案以及提高患者的预后产生巨大的影响。现阶段已有不少的研究利用CT或MRI影像组学的方法对HCC MVI进行预测，并且都取得了很好的效果。本文将对目前关于HCC MVI影像组学预测的研究进展进行阐述。

【关键词】肝细胞癌；微血管侵犯；磁共振成像；计算机断层成像；影像组学
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Research Status of Radiomics for Predicting Microvascular Invasion in Hepatocellular Carcinoma*

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ABSTRACT
Hepatocellular carcinoma (HCC) is one of the most common malignant tumors that pose a great threat to human health, and its treatment has always been a challenge due to its high morbidity and mortality rates and poor prognosis. Microvascular invasion (MVI) has been shown to be an important cause of postoperative recurrence and poor prognosis in hepatocellular carcinoma in several studies. However, the diagnosis of MVI is mainly confirmed by histopathologic examination of hepatocellular carcinoma after surgery. If MVI could be predicted before surgery, it would have a great impact on guiding individualized treatment plans and improving patients' prognosis. At this stage, many studies have been conducted on the prediction of HCC MVI using CT or MRI radiomics, and all of them have achieved very good results. In this paper, we will describe the current research progress on the radiomic prediction of HCC MVI.
Keywords: *Hepatocellular Carcinoma; Microvascular Invasion; Magnetic Resonance Imaging; Computed Tomography; Radiomics*

肝细胞癌(hepatocelluar carcinoma，HCC)的治疗一直是困扰我们的难题。目前，肝细胞癌的治疗方法主要有以下几种：肝移植、手术切除以及射频消融等[1-2]。多项研究表明，肝细胞癌患者进行手术切除和肝移植术后的复发率很高[3-5]。微血管侵犯(microvascular invasion，MVI)是通过显微镜观察到在内皮细胞衬附的血管腔内存在的癌细胞巢团[6]。目前MVI已经被研究证实是肝细胞癌术后复发以及预后不良的重要原因[7]。由于MVI仅在显微镜下可见，所以必须通过术后病理学检查才能确诊，在术前我们也很难通过传统的影像学方法，如计算机断层成像(computed tomography，CT)、磁共振成像(magnetic resonance imaging，MRI)来确诊MVI。因此，如果能够早期发现HCC MVI，就可以降低复发率、提高患者的预后，帮助患者制定个体化的治疗方案。

影像组学作为近年来备受关注的一种新兴技术，它能从常规的影像学成像方法(如CT、MRI等)中实现高通量的定量成像特征或纹理特征的自动提取[8-10]，为我们了解肿瘤的异质性以及微环境提供了重要的途径。影像组学研究的主要流程包括：图像采集、肿瘤分割、特征提取和分类器建模[11]，下文将从不同研究对以上几个步骤的不同处理方式来进行阐述。

1 基于不同图像采集方式的影像组学研究

CT和MRI成像是常规的影像学图像采集方法，由于两者都具备平扫和增强扫描的模式，我们便可以通过HCC增强扫描不同时期的表现，实现HCC的诊断，因此目前对HCC MVI影像组学的研究大多采用增强扫描模式。对于CT而言，HCC在增强CT上的特征性强化方式，使我们对HCC的诊断更加准确与高效。大量的研究通过提取CT增强扫描三个时期的特征对HCC MVI进行了预测[12-21]。其中，Ma[12]等人的研究通过对动脉期(arterial phase，AP)、门静脉期(portal venous phase，PVP)、延迟期(delayed phase，DP)三个时期的特征进行提取，并建立三个时期独立的影像组学模型，得出PVP时期的模型具备最高的预测效果(AUC=0.793)。Yao[19]等人使用相似的方法得出DP时期的模型预测效果最高(AUC=0.80)。这种差异可能与病例选择偏倚相关。目前哪个时期对HCC MVI的预测效果最好还需不断探索。

相比于CT，磁共振具备更多的序列，对于HCC MVI的预测也有更多的方式方法。常见MRI序列有T1加权成像(T_1-weighted imaging，T_1WI)、T2加权成像(T_2-weighted imaging，T_2WI)、弥散加权成像(diffusion-weighted imaging，DWI)，常规增强MRI扫描也能获得AP、PVP、DP三期图像，大量的学者基于此特点进行了HCC MVI影像组学的研究[22-27]，Nebbia[22]等人通过提取五个MRI序列(T_1WI、T_2WI、DWI、AP和PVP)中每个序列的影像组学特征，建立了单序列影像组学模型，最终得出表现最好的单序列模型是T_2WI序列模型(AUC=0.808)和PVP序列模型(AUC=0.792)。同时我们还观察到不同的增强MRI对比剂也会影响影像组学模型的预测效能。钆二酸二钠(GD-EOB-DTPA)是肝胆特异性对比剂，目前，在增强MRI扫描中得到了广泛的应用，GD-EOB-DTPA相比于普通胞外钆对比剂来讲，可以通过减慢造影剂注射速率来延长强化的持续时间，因此在注射对比剂20min后，能形成特有的肝胆期(hepatobiliary phase，HBP)图像。大量的研究也证明了HBP序列的预测能力大于其他序列的预测能力[28-29]，并且zhang[30]等人的研究

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在单序列的基础上，将所有序列融合起来组成的多序列融合模型是表现最好的模型，在训练和验证数据集的AUC分别为0.889和0.822，显著提高了预测能力。

2 基于不同感兴趣区(region of interest，ROI)的影像组学研究

大量的研究都是基于肿瘤本身，在肿瘤边缘进行ROI的勾画，建立HCC MVI的影像组学模型[31-32]，有研究发现肿瘤边缘被侵犯时，MVI发生的概率更大[33]。并且MVI通常发生在距离肿瘤边界10mm以内[34]。有研究者通过划分不同的ROI来建立HCC MVI影像组学模型。Feng[35]等人第一个通过Gd-EOB-DTPA增强MRI，建立了术前预测MVI的肿瘤联合瘤周影像组学模型，结果显示，肿瘤内和瘤周联合影像组学模型在测试组中的AUC、敏感性和特异性分别为0.83、90%和75%。Zhang[36]等人同样建立肿瘤内和肿瘤周围区域(10mm)的MRI影像组学模型，也取得的很好的预测效果(AUC=0.825)。有学者同样利用CT也建立了肿瘤和瘤周10mm的联合CT影像组学模型，最终获得的AUC=0.780[37]。但上述研究均为一个ROI，即肿瘤联合瘤周10mm。肿瘤联合瘤周的模型预测效能是否一定高于基于肿瘤本身的模型，瘤周外扩的大小是否也会影像预测效能，大量的研究基于上述疑问进行了探讨，未得出一致结论，Yang[38]等人建立了瘤周10mm的预测模型，得出肿瘤联合瘤周模型的辨别能力并不优于基于肿瘤本身的模型。Chong[28]等人划分了不同的ROI(肿瘤50%、肿瘤、肿瘤联合瘤周5mm、肿瘤联合瘤周10mm、肿瘤联合肝脏背景)，并且对不同的模型进行了预测，最终得出肿瘤联合瘤周10mm及肝脏背景的预测效能高于其他模型。Zhang[39]等人的研究划分了最多的瘤周距离(分别为瘤周2mm、4mm、6mm、8mm、10mm、12mm、14mm)来建立CT影像组学模型，最终得出处于PVP肿瘤联合瘤周12mm的模型预测效果最好(AUC=0.81)。现阶段，预测HCC MVI影像组学模型最佳的瘤周边缘大小还未得出一致结论，仍需要大量研究进行探索。

3 基于不同机器学习方法的影像组学研究

传统的机器学习方法主要有逻辑回归、随机森林、支持向量机、K近邻、决策树、梯度提升决策树等[40]。其中逻辑回归是最常用于影像组学的机器学习方法。采用不同的机器学习方法建立模型同样也会对HCC MVI的预测效果产生影响。Dai[41]等人比较了逻辑回归、支持向量机、随机森林和梯度提升决策树四种建模方式在预测HCC MVI的效果差异，发现基于梯度提升决策树增强磁共振HBP图像的影像组学模型在MVI术前预测方面表现优于逻辑回归、支持向量机和随机森林(AUC分别为0.895、0.850、0.834、0.884)。Gao[42]等人同样使用了四种机器学习方法: 逻辑回归、逻辑回归、随机森林和自适应增强来建立HCC MVI的术前预测MRI模型，最终发现使用逻辑回归或支持向量机的模型AUC值最高。Ni[43]等人将不同的机器学习方法与不同的降维方法进行随机组合，最终得出使用绝对收缩和选择算子(least absolute shrinkage and selection operator，LASSO)降维联合梯度提升决策树建立的CT影像组学模型的准确性最高(84.48%)。尽管使用了不同的机器学习方法得出的结果不完全一致，但都证明了选择不同的机器学习方法会对结果产生影响。因此，我们需要尽可能选择预测效能最优的分类器建立模型来提高预测效能。

4 基于临床影像学独立预测因素的联合影像组学研究

不少研究证明了临床上独立的特征指标可以有效预测HCC MVI，如甲胎蛋白、转氨酶、肝功能分级、年龄、性别等[44-46]。同样地，HCC在CT或MRI上的影像学特征，如肿瘤最大径、动脉期瘤周强化、肿瘤包膜特点等也被证明为HCC MVI的独立危险因素[47-48]。目前，大多数基于HCC MVI影像组学的研究都会联合上述临床和影像学上的独立预测因素来建立临床影像组学联合模型，以此来提升HCC MVI的预测效能，并且这在多项研究中得到了证实。

5 总结与展望

目前，已有大量的研究使用影像组学的方法来预测HCC MVI，并且通过上文所阐述的不同方法途径：如使用CT或MRI、划分不同的ROI、使用不同的机器学习方法，并且在此基础上联合临床影像学预测因素建立模型，都取得了很好的预测效果，说明了对于HCC MVI的预测来说，影像组学方法具有可行性。但以上研究多为单中心研究，对于存在病例数较少，不同扫描机器差异等不足，在未来可以进行更多的多中心研究来提高结果的准确性。近年来，深度学习(deep learning，DL)模型也被用于HCC MVI的预测，DL主要是通过使用多层神经网络来自动学习任务中的图像特征。多项研究表明它能表现出比影像组学更优越的预测性能[49-52]。其中，Song[50]等人的研究表明在测试队列中，DL模型的AUC值明显高于影像组学模型，AUC值分别为0.915和0.731。这将会对提高HCC MVI术前预测的准确性和治疗的及时性提供很大的帮助。除此之外，现阶段大多数研究都只利用影像组学模型预测术前有无HCC MVI，但我国原发性肝癌规范化病理诊断指南将MVI进行了具体的病理分级：M0、M1、M2[6]。如果可以通过建立影像组学模型预测MVI具体分级，将会对提高HCC患者的预后和制定个体化的治疗方案提供新的方向。

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