· 综述 ·

Research progresses of radiomics and deep learning for predicting prognosis of hepatocellular carcinoma

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[**Abstract**] The prognosis of hepatocellular carcinoma (HCC) may be different in a great degree, and accurate predicting prognosis is helpful for carrying out individualized and precise treatment. With the developments of artificial intelligence, radiomics and deep learning (DL) were widely used, providing valuable information for diagnosis and treatment of HCC through mining higher dimensional quantitative features on medical images. The research progresses of radiomics and DL for predicting prognosis of HCC were reviewed in this article.

[**Keywords**] carcinoma, hepatocellular; prognosis; deep learning; radiomics
DOI: 10.13929/j.issn.1672-8475.2024.05.011

影像组学及深度学习预测肝细胞癌预后研究进展

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[**摘　要**] 肝细胞癌（HCC）预后差异较大，准确预测预后有助于展开个体化精准治疗。随着人工智能的发展，影像组学及深度学习（DL）运用日渐广泛，可通过挖掘医学图像中的高维度肿瘤定量特征而为诊断与治疗HCC提供更多信息。本文就影像组学及DL预测HCC预后研究进展进行综述。

[**关键词**] 癌，肝细胞；预后；深度学习；影像组学
[**中图分类号**] R735.7；R445　[**文献标识码**] A　[**文章编号**] 1672-8475(2024)05-0302-05

肝细胞癌（hepatocellular carcinoma，HCC）是最常见的原发性肝癌[1]，亦是全球癌症相关死亡的主要原因之一[2]。目前主要根据HCC肿瘤负荷、患者肝功能及临床表现制定治疗方案，包括肝切除术、射频消融（radiofrequency ablation，RFA）及TACE等[3]，但总体预后差强人意[4]。制定个体化、规范化综合治疗HCC方案有助于提高患者生存质量、延长生存期。利用影像组学及深度学习（deep learning，DL）方法可从CT、MRI、PET及超声等医学图像中提取定量数据用于诊断及指导治疗决策[5]。本文就影像组学及DL预测HCC预后研究进展进行综述。

1　组织学

1.1　微血管侵犯（microvascular invasion，MVI）　MVI与HCC术后复发及患者远期生存率降低密切相关。XU等[6]联合应用基于CT图像提取的HCC MVI相关影像组学特征获得的影像组学评分（Radscore）、临床因素及影像学评分构建的预测模型预测测试集HCC MVI的受试者工作特征曲线下面积（area under the curve，AUC）为0.89。HU等[7]报道，基于声像图获取的Radscore与甲胎蛋白（α-fetoprotein，AFP）及肿瘤大小均可作为HCC MVI的独立预测因子。FENG等[8]基于钆塞酸二钠（gadolinium ethoxybenzyl

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[**收稿日期**] 2024-01-10　[**修回日期**] 2024-04-06

diethylenetriamine pentaacetic acid，Gd-EOB-DTPA）增强MRI构建影像组学模型，发现结合瘤内和瘤周影像组学特征模型预测MVI效能优于单纯瘤内影像组学模型，原因可能与MVI主要发生于肿瘤边缘有关；其他研究[9-10]也得到相似结论，但目前对于为获最佳预测效能所应覆盖的瘤周范围尚未达成统一认识。

1.2 预后不良基因表达 细胞角蛋白（cytokeratin，CK）19阳性HCC侵袭性更高，且更易发生耐药，出现淋巴结转移、复发等不良预后，患者生存率更低[11]。CHEN等[12]基于术前增强MRI构建的DL影像组学模型识别外部验证集HCC中CK19的AUC为0.78；纳入可预测CK19表达的影像组学特征、瘤内出血和瘤周低信号等独立危险因素后建立的列线图预测无复发生存期（recurrence free survival，RFS）的C指数为0.71。

磷脂酰肌醇蛋白聚糖-3（glypican-3，GPC3）与肿瘤进展有关，可作为免疫治疗HCC靶点；GPC3靶向单克隆抗体和GPC3靶向嵌合抗原受体T细胞可有效杀灭GPC3阳性HCC肿瘤细胞[13]。GU等[14]联合AFP与增强MR T1WI影像组学特征建立的列线图可有效预测HCC的GPC3表达。CHONG等[15]报道，利用临床-影像组学模型可预测直径≤5 cm HCC的GPC3表达。

HCC高表达Ki-67与其高侵袭性及高早期复发率有关[16]。FAN等[17]于动脉期、门静脉期及肝胆期增强MRI中提取影像组学特征，建立动脉期Radscore和血清AFP水平联合模型，其预测验证集HCC Ki-67表达的AUC为0.86。LI等[18]发现基于动脉期、门静脉期和肝胆期增强MRI的纹理分析有助于预测HCC Ki-67表达，并可能为寻找HCC病理学标志物提供支持。

2 预测疗效及结局

影像组学及DL模型具有预测HCC预后的潜力，借此可优化治疗方案、改善临床结局，或可为现有风险评价标准提供增量价值。

2.1 预测治疗反应 影像学引导TACE、RFA、经动脉放射栓塞术（transarterial radioembolization，TARE）等可用于局部治疗HCC、尤其中晚期HCC；治疗后主要基于CT或MRI、根据改良实体瘤疗效评价标准（modified response evaluation criteria in solid tumors，mRECIST）评价疗效[19-20]。CHEN等[21]对来自多中心的585例经首次TACE后HCC患者的CT图像以半自动方法分割瘤内和瘤周（10 mm）ROI，提取其影像组学特征并构建临床-影像组学模型，该模型预测内部及外部验证集治疗反应的AUC分别为0.94及0.90。另一项回顾性多中心研究[20]采用残差网络（residual network 50，ResNet50）迁移学习方法基于中期HCC患者CT图像构建预测TACE治疗反应的DL模型，其预测验证集完全缓解（complete response，CR）、部分缓解（partial response，PR）、疾病稳定（stable disease，SD）及疾病进展（progression disease，PD）的准确率达82.8%～85.1%。数字减影血管造影（digital subtraction angiography，DSA）可实时动态观察病变位置、为介入操作提供导航及动脉供血等信息，亦可用于评价疗效。ZHANG等[22]纳入605例以TACE作为初始治疗的中期HCC患者，通过实时自动分割DSA图中的肿瘤ROI预测TACE治疗反应，其在外部验证集的AUC为0.82。AUJAY等[19]以影像组学分析局部晚期HCC患者TARE前、后增强MRI，发现根据影像组学特征可预测早期治疗反应。

目前靶向治疗与免疫治疗的重要性日益凸显，但尚缺乏可准确预测全身治疗效果的临床或分子标志物。TIAN等[23]基于MRI构建影像组学及DL特征联合模型，5折交叉验证显示其预测HCC程序性细胞死亡配体1（programmed cell death ligand 1，PD-L1）表达水平的AUC达0.90。另有研究[24-25]尝试采用影像组学预测抗程序性细胞死亡受体1（programmed cell death protein 1，PD-1）治疗HCC效果，结果显示影像组学具有良好预测价值；但上述研究纳入样本量均较小，且缺乏外部验证。此外，MULÉ等[26]提出治疗前HCC CT纹理特征可用于预测患者接受索拉非尼治疗后生存率；BO等[27]报道影像组学机器学习模型预测不可切除HCC对仑伐替尼单药治疗反应具有良好表现。

2.2 预测肿瘤复发 影像组学分析对预测HCC经治疗后早期复发具有良好效能。GAO等[28]基于MRI影像组学特征及DL特征构建的联合模型可有效分层预测HCC切除术后早期复发风险。JI等[29]基于机器学习框架筛选于瘤内及瘤周增强CT提取的影像组学特征，以之建立的Cox风险预测模型可有效预测根治性切除术后HCC复发风险并进行风险分级。

ZHANG等[30]认为多参数MRI影像组学模型对预测直径≤3 cm HCC RFA后2年内（早期）复发具有较高价值。LV等[31]基于治疗前对比增强T1WI（contrast-enhanced T1WI，CE-T1WI）提取并筛选影像组学特征以计算Radscore，以之联合肿瘤形状、表观弥散系数（apparent diffusion coefficient，ADC）、弥散

加权成像(diffusion weighted imaging, DWI)信号强度及信号强度差等临床及影像学因素构建的联合模型预测RFA后侵袭性节段内复发的效能及相应列线图的临床净收益均较高；WEN等[32]基于直径≤3 cm HCC术前或RFA前增强MRI影像组学特征及临床危险因素构建的预测模型亦得到相似结果。SHAN等[33]对比纳入与未纳入CT图像中瘤周2 cm区域建立的影像组学模型，发现前者预测HCC治疗后早期复发效能及校准度均更高。

肝移植(liver transplantation, LT)为治疗HCC的有效根治性方法，既往多依据肿瘤大小进行临床分配。影像组学与DL模型有望预测HCC LT后复发风险并辅助LT分配，将LT适应证扩展到肿瘤负荷更高的HCC患者。HE等[34]发现MRI影像组学特征可参与预测LT后HCC患者RFS。IVANICS等[35]认为以TACE前增强CT构建的影像组学模型可用于预测LT后PD或复发等不良结局；NIE等[36]提出基于CT影像组学分析HCC瘤内异质性(intratumor heterogeneity, ITH)可预测LT后复发风险。

2.3　预测生存期　基于CT、MRI及PET/CT的定量影像组学分析模型可有效预测HCC经TACE后预后[37-38]。刘颖等[39]结合动脉期瘤周3 mm与静脉期瘤体CT影像组学特征构建联合模型，发现其预测TACE后HCC患者生存期的效能与稳定性均较好。MENG等[40]基于增强CT提取动脉期和门静脉期HCC瘤内及瘤周区域影像组学特征，联合瘤灶数(＜4或≥4)构建的影像组学-临床联合模型预测测试集TACE后HCC患者总生存期(overall survival, OS)的AUC为0.70，并认为CT影像组学特征可作为TACE后HCC患者生存期的独立预测因子。LIU等[41]同样认为CT纹理参数等HCC影像组学特征为其OS的独立预测因素。MÜLLER等[42]基于CT利用卷积神经网络自动分割并获取脾脏体积，发现其预测经TACE初治HCC患者生存率的效能高于基于二维CT所获脾脏大小。KIM等[43]基于术前增强MRI提取包含瘤周3 mm的影像组学特征，构建影像组学模型并与术后临床病理学模型比较，发现二者预测HCC切除术后2年内患者无病生存期(disease free survival, DFS)的效能相当。LI等[37]纳入巴塞罗那临床肝癌分期0及A期HCC患者，基于^{18}F-FDG PET/CT提取肿瘤影像组学特征，发现5个PET纹理特征、6个CT纹理特征与肿瘤MVI相关；该研究同时发现，以影像组学特征建立列线图，并与国际标准化比值和血清总胆红素相结合，可有效预测患者DFS。

3　小结

影像组学特征或为HCC预后潜在标志物，影像组学及DL分析对于预测HCC预后具有巨大价值，包括显示遗传特征、预测治疗反应、预测早期复发及生存率等，有望改善HCC多学科管理、辅助优化个体化治疗。目前相关临床应用尚面临挑战，包括分割ROI及提取特征尚未实现自动化及标准化等，且已有研究多为单中心分析、样本量较小且缺乏外部验证等，均有待后续逐步完善。

利益冲突：全体作者声明无利益冲突。

作者贡献：段正新查阅文献、撰写文章；赵卫指导、审阅文章；易根发查阅文献、修改文章。

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