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·文献综述·

# 术前预测肝细胞癌并微血管侵犯的研究进展

陈洁 综述 黎乐群 审校

（广西医科大学附属肿瘤医院 肝胆外科，广西 南宁 530021）

**摘 要** 肝细胞癌（HCC）是常见恶性肿瘤之一，手术和肝移植是目前可治愈的手段，但是术后易复发，预后较差。微血管侵犯是（MVI）独立的预后因素，其术前诊断成为研究的热点。笔者就目前的术前预测 HCC 并微 MVI 的研究进展进行综述。

**关键词** 癌，肝细胞；肿瘤侵润；微血管；综述文献
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# Research progress of preoperative predicting microvascular invasion of hepatocellular carcinoma

CHEN Jie, LI Lequn

*(Department of Hepatobiliary Surgery, Affiliated Tumor Hospital, Guangxi Medical University, Nanning 530021, China)*

**Abstract** Hepatocellular carcinoma (HCC) is one of the common malignancies, for which, surgical resection and liver transplantation may be potentially curative remedies but the prognosis remains poor due to a high likelihood of postoperative recurrence. Microvascular invasion (MVI) is an independent prognostic factor, and its preoperative diagnosis has become a hot topic in the field of research. Here, the authors review the current research progress in preoperative prediction of HCC with MVI.

**Key words** Carcinoma, Hepatocellular; Neoplasm Invasiveness; Microvessels; Review
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肝细胞癌（HCC）是世界上最常见的恶性肿瘤之一，特别是我国广西地区，肿瘤致死率高居第三位[1]，该肿瘤具有侵袭肝内血管的倾向，导致肝内和肝外转移[2]。外科手术治疗和肝移植（LT）是目前最主要的HCC治疗手段[3]，然而，手术切除和肝移植的预后仍无法达到预期效果，其中最需要克服的难题就是术后复发[4]。手术切除后、肝移植后5年复发率分别高达70%、35%[5]。大血管侵犯和微血管侵犯（microvascular invasion，MVI）均与肿瘤分期和疾病进展有关。通常大血管肿瘤侵犯可通过影像学检查确诊[6]。MVI是HCC发生发展过程中出现的一种病理征象，是肿瘤早期转移的标志[7]。但MVI的临床意义常被低估，认为MVI是一种较为温和的肿瘤侵袭形式，随着对MVI的研究认识和其对预后的不良影响，MVI已经成为HCC研究的热门话题，而目前仅能通过术后标本的组织病理学检查诊断[8]，这对于术前治疗方案的制定

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**作者简介：** 陈洁，广西医科大学附属肿瘤医院副教授，主要从事 HCC 基础与临床方面的研究。
**通信作者：** 黎乐群， Email: 903488911@qq.com

具有滞后性。因此，术前合理预测MVI对HCC患者个体化治疗方案的制定及其远期预后的评估具有重要意义[9]。本文综合近年来对HCC术前预测MVI的文献报道，予以综述。

## 1 MVI

MVI的诊断标准尚未统一。Sumie等[10]指出只要在门静脉或肝静脉系统发现肿瘤细胞即可诊断为MVI。不过，他们没有考虑到胆管和淋巴管侵犯以及血管侵犯到肿瘤边缘的距离。目前，较多学者[11]对MVI定义为显微镜下于内皮细胞衬覆的血管腔内见到癌细胞巢团的观点表示认可。MVI是一种由多因素参与导致的复杂的生物过程，包括HCC与微环境的相互作用，以及与宿主状态（免疫、内分泌和代谢等）[12]。目前机制尚未明确。

## 2 术前预测 MVI 的重要性

大量研究[13]表明MVI可反映HCC早期转移能力和侵袭程度，并且可作为HCC预后的独立危险因素。在HCC合并MVI时，患者总生存率及3年无复发率都将缩短[3,14]。近年来对MVI的研究越来越具体化，主要集中在MVI多发位置、对微血管侵犯程度以及微血管数目等[15-17]；Parfitt等[18]研究甚至将淋巴管侵犯也归纳为MVI。随着对MVI研究范围的扩展，目前报道的HCC的MVI发生率明显升高。Lim等[19]通过对225例HCC切除术患者的调查研究发现，MVI阳性组中位复发时间（12.0个月）显著低于MVI阴性组（42.2个月）；Hou等[20]研究结果表明，MVI不仅是限制首次术后生存的危险因素（*HR*=2.62，95% *CI*为2.15~3.19），再次手术也具有同样重要作用（2次术前MVI均阳性：*HR*=4.79，95% *CI*=2.54~9.53；首次术前MVI阴性、再次复发术前MVI阳性：*HR*=4.02，95% *CI*=2.27~7.13）。<2 cm早期小HCC通常认为手术切除的预后效果较好[21]，但Yamashita等[22]研究149例<2 cm早期小HCC中发现43例合并MVI的患者接受HCC切除后，1年复发率为23.3%，显著大于不伴有MVI的复发率（7.5%）。Roayaie等[23]研究证实扩大手术切缘（>1 cm）可以减少HCC伴有MVI患者的肿瘤复发。Zhou等[24]研究也表明肝解剖切除可见降低HCC并MVI患者的术后复发率。因此，如果术前可以确定MVI的风险，可以术前做出解剖切除或非解剖切除以及手术切缘的宽度的合理选择，在术中更具针对性的外科治疗策略，对提高生存时间具有重要价值[25-26]。

目前，MVI的诊断主要依靠手术标本的病理检查。术前肝脏穿刺活检诊断MVI准确性低，不确定因素多，且属于有创检查，患者接受度差。由此导致的结果就是，由于无法依据MVI信息制定扩大肝切缘的治疗方案，具有明显的滞后性，使患者失去延长生存期的机会[27]。同时，MVI常发生于晚期HCC患者，而在早期HCC中发生率相对较低，然而早期HCC才是接受根治性治疗的最佳适应指征，因此术前预测早期HCC MVI有着更大的临床应用价值。随着诊疗设备及医学理论的发展，MVI的术前预测也得到巨大进步，目前比较公认的检测方法主要为影像学、血清学及信号通路检查。

## 3 用术前影像学特征预测 MVI

### 3.1 CT 预测 MVI

CT是最早用于预测HCCMVI的影像学方法之一。Eguch等[28]研究表明，HCC瘤灶单节结型较之于其他分型HCC（多节结型或单结节结外生长型）发生MVI的风险率更低。张俊等[29]研究进一步指出，HCC的常见CT征象（肿瘤最大直径、癌组织边缘强化程度、肿瘤包膜及肿瘤形态）中，只有肿瘤形态对预测MVI有意义，其诊断的灵敏度、特异度、准确率分别为76.7%、75.0%、76.0%。此外，李文柱团队[30]还验证了能谱CT对预测微血管侵犯的可行性，该研究指出动脉期标准碘基值（NIC-a）与HCC微血管密度（MVD）呈中度相关（$r$=0.507，$P$<0.05）。杨创勃等[31]也发现能谱CT扫描对评估微血管侵犯具有重要价值，进一步证实能谱CT碘基值与微血管侵犯的相关性。Banerjee等[5]研究更是将CT对MVI的预测延生到分子影像学层面，该实验通过CT靶向性MVI高危基因（91-gene）来评估静脉侵润程度（RVI），并利用RVI诊断MVI的准确率、灵敏度、特异度分别为89%、76%、94%，RVI阴性组3年HCC切除术后无复发率为62%，较之RVI阳性组（无复发率27%）高出1倍以上。可见，CT对HCC形态学的判断以及MVI分子标记物的示踪，为MVI的预测提供了一个新的思路，在临床医师制定HCC治疗策略时应该特别注意。

 

### 3.2 MRI 预测 MVI

MRI因其较高的软组织分辨率及功能成像的日渐成熟，该技术用于MVI的预测的研究也得到较大进展。Chandarna等认为[32]，HCC瘤灶形态的不规则是预测MVI得唯一指标，包括病理及AFP在内的其他临床特征都与MVI不相关。MRI对HCCMVI的预测除了依据瘤灶形态学指征外，MRI功能学成像同样具有重要诊断价值。Xu等[33]利用磁共振扩散加权成像对HCC微血管侵犯的研究结果表明，以表观弥散系数（ADC）<$1.227\times10^{-3}$ s/mm$^2$作为最佳诊断阈值时，其灵敏度、特异度分别为66.7%、78.6%。Renzulli等[34]研究表明，同时存在HCC的3个危险征象（肿瘤边缘不光整、边缘强化以及静脉侵润）时，在不计肿瘤大小的情况下，其诊断阳性预测值可达95%。由此可知，MRI对HCCMVI的预测同样具有重要价值。

## 4　血清蛋白标志物预测 MVI

该方法主要是检测血清中某种HCC特异性抗原表达量来预测MVI发生，现在研究较多的有异常凝血酶原（DCP）和AFP等。Poté等[35]发现HCC患者血清DCP>90 mAU/mL可作为MVI的独立预测因素（*HR*=3.5，95% *CI*=1.08~11.8），该诊断阈值对应的灵敏度、特异度分别为70%、63%，若联合组织DCP检查，则灵敏度、特异度可提高到87%、90%。Dumitra等[36]研究发现AFP斜率对预测MVI及HCC的复发具有重要意义。Zhao等[37]以多结节HCC进行亚组分析，发现GGT>130 U/L时，MVI阳性率比MVI阴性率高出1倍多。这种方案局限性是特异性不强，例如DCP和AFP在慢性肝炎和肝硬化等非HCC患者的血清同样呈高表达[38]，容易造成诊断重叠。目前尚未发现对MVI特异的血清蛋白标志物。

## 5　用 HCC 信号通路蛋白、mRNA 或基因预测 MVI

这一思路的创新性在于着眼于HCC发生机制，通过对病理组织的样本检测，发现与HCC关系密切的信号通道基因或蛋白发生了改变，这其中的一些分子生物学指标被认为与MVI的存在有关[39]。Poté等[40]利用质谱成像发现组蛋白4的修饰物（H4K16ac与H4K20me2）在MVI阳性组高表达，明显不同于MVI阴性组。Yu等[41]发现抗血清热休克蛋白70在MVI阴性患者中显著高于MVI阳性患者，由此推测抗血清热休克蛋白70可作为MVI阴性患者血清学标志物。Ding等[42]应用Li-钙黏蛋白（Li-cadherin）与其他黏附分子结合，预测HCC患者的MVI和预后。Mínguez等[43]发现了35个基因标记（14个基因高表达和21个基因低表达）与血管侵犯有关，对MVI预测的准确度为69%。考虑到低特异性、技术复杂性和高成本，这些方法仍处于研究阶段，在目前较短时间内难以将基础研究转化为临床应用[44]。

## 6　结　语

综上所述，MVI对HCC的治疗方式及预后发展都有着重大作用，现有的MVI术前预测技术各有所长又各有短板，故而在临床推广应用上应该综合考虑，使得建立一个整合多个预测因子的临床预测模型逐渐成为现实，为减低HCC患者术后复发及转移，改善患者预后等方面带来福祉。

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