

肝细胞癌伴微血管侵犯诊断和治疗 中国专家共识(2024 版)

中国医师协会肝癌专业委员会

通信作者:沈锋,海军军医大学第三附属医院,上海 200438,Email:shenfengehbh@sina.com;程树群,海军军医大学第三附属医院,上海 200438,Email:chengshuqun@aliyun.com

【摘要】 肝细胞癌(以下简称肝癌)是我国常见的恶性肿瘤之一,手术切除是首选的治疗方法,但术后复发转移率高。目前证据表明微血管侵犯(MVI)是导致肝癌复发转移的独立危险因素,但是目前国际上对于 MVI 的诊断、分型、预测和治疗仍存在较多争议。为更好地指导肝癌伴 MVI 的诊断和治疗,中国医师协会肝癌专业委员会组织国内相关领域专家,经过多次讨论和修改,形成《肝细胞癌伴微血管侵犯诊断和治疗中国专家共识(2024 版)》,以供国内同行参考。

【关键词】 肝细胞癌; 微血管侵犯; 诊断; 治疗; 共识

基金项目:国家重点研发计划(2022YFC2503705);国家自然科学基金(82072618);上海市卫健委“重中之重”项目(2023ZZ02005)

Chinese expert consensus on the diagnosis and treatment of hepatocellular carcinoma with microvascular invasion (2024 edition)

Chinese Association of Liver Cancer of Chinese Medical Doctor Association

Corresponding authors: Shen Feng, the Third Affiliated Hospital of Naval Medical University, Shanghai 200438, China, Email: shenfengehbh@sina.com; Cheng Shuqun, the Third Affiliated Hospital of Naval Medical University, Shanghai 200438, China, Email: chengshuqun@aliyun.com

【Abstract】 Hepatocellular carcinoma (hereinafter referred to as liver cancer) is one of the most common malignant tumors in China. Surgical resection is the preferred treatment for liver cancer, but the postoperative recurrence and metastasis rates are quite high. Current evidence shows that microvascular invasion (MVI) is an independent risk factor for postoperative recurrence and metastasis of liver cancer, but there are still many controversies about the diagnosis, classification, prediction and treatment of MVI over the world. The Chinese Association of Liver Cancer of Chinese Medical Doctor Association organizes domestic experts in related fields to form the *Chinese Expert Consensus on the Diagnosis and Treatment of Hepatocellular Carcinoma with Microvascular Invasion (2024 Edition)* after many discussions and revisions, in order to better guide the diagnosis and treatment of Liver Cancer with MVI and for reference by domestic peers.

【Key words】 Hepatocellular carcinoma; Microvascular invasion; Diagnosis; Treatment; Consensus

Fund programs: National Key Research and Development Program (2022YFC2503705); National Natural Science Foundation of China (82072618); Shanghai Municipal Health Commission "Top Priority" Project (2023ZZ02005)

肝细胞癌(以下简称肝癌)是我国第 5 种最常见的恶性肿瘤,每年新发病例约为 40 万例,死亡率仅次于肺癌,居全部恶性肿瘤死亡原因的第 2 位^[1]。

手术切除仍是我国肝癌的首选治疗方法,但术后 5 年总体复发率高达 70%^[2-3];肝移植术后 5 年复发率为 4.3%~57.8%^[4-7]。肝癌极易侵犯血管造成血行

DOI:10.3760/cma.j.cn115610-20240125-00041

收稿日期 2024-01-25

引用本文:中国医师协会肝癌专业委员会.肝细胞癌伴微血管侵犯诊断和治疗中国专家共识(2024 版)[J].中华消化外科杂志,2024,23(2):153-164. DOI:10.3760/cma.j.cn115610-20240125-00041.



转移,可能是造成肝癌复发转移的主要原因。微血管侵犯(microvascular invasion, MVI)主要指仅能在显微镜下观察到、在覆衬有内皮细胞的微小血管腔内存在的癌细胞巢团,多见于肿瘤包膜内和癌旁肝组织内的门静脉微小分支。MVI是导致肝癌复发转移的独立危险因素,其生物学特性和预后作用日益受到重视,但目前国际上对于MVI的诊断、分型、预测和治疗仍存在较多争议。为此,中国医师协会肝癌专业委员会基于现有的循证医学证据,尤其是我国学者在肝癌伴MVI领域取得的研究成果,组织共识委员会的多学科专家进行多次讨论,形成《肝细胞癌伴微血管侵犯诊断和治疗中国专家共识(2024版)》(以下简称共识)。随着新的循证医学证据不断出现,本共识将随之进行更新和完善。

本共识中循证医学证据等级评估参照证据评价与推荐意见分级、制定和评价(grading of recommendations, assessment, development and evaluation, GRADE)^[8-9],见表1。证据评价分级的指导原则法(<http://www.gradeworkinggroup.org/>)和《牛津循证医学中心2011版》。专家推荐的强度参照GRADE对推荐意见分级的指导原则。本共识已在国际实践指南注册与透明化平台(<http://www.guidelines-registry.cn/>)注册,注册号:PREPARE-2024CN185。

表1 证据评价与推荐意见分级、制定和评价证据质量与推荐强度分级

Table 1 Grading of recommendations assessment, development and evaluation

类别	具体描述
证据质量分级	
高(A)	非常有把握观察值接近真实值
中(B)	对观察值有中等把握:观察值有可能接近真实值,但也有可能差别很大
低(C)	对观察值的把握有限:观察值可能与真实值有很大差别
极低(D)	对观察值几乎没有把握:观察值与真实值可能有极大差别
推荐强度分级	
强(1)	明确显示干预措施利大于弊或弊大于利
弱(2)	利弊不确定或无论质量高低的证据均显示利弊相当
GPS(Good practice statement)	基于非直接证据或专家意见/经验形成的推荐

一、MVI的诊断和分型

(一)发生率、病理诊断和分型

已有研究结果显示:肝癌MVI的发生率为17.0%~

93.4%^[10-21]。MVI发生率与肿瘤长径呈正相关,长径<3 cm的肝癌MVI发生率为17.0%~40.6%^[16,18,21-26];长径为3~5 cm的肝癌为31.0%~42.5%^[22-23,27-28];长径>5 cm的肝癌为46.2%~93.4%^[23,27,29-33];多发性肝癌为9.9%~81.3%^[4,13,17,23,34-37];符合米兰标准的肝癌为9.9%~54.0%^[4,13,38-39]。

已有研究结果显示:MVI的部分病理特征,例如侵犯微血管的数量^[40-43]、分布情况^[43-45]、巢团内癌细胞计数^[40,43,46]、侵袭性分型^[42]和侵犯具有肌层的微血管^[44]等,均显著影响肝癌预后。Roayaie等^[44]将MVI定义为显微镜下微血管可见肿瘤细胞,并依据侵犯的微血管是否存在肌层,以及距肿瘤≥1 cm 2个危险因素将MVI分为B1型:存在MVI但无其他危险因素;B2型:MVI合并1个危险因素;B3:MVI合并2个危险因素。也有学者将MVI定义为镜下发现肝癌侵犯门静脉、肝静脉、微动脉及淋巴管中的一个或多个^[38,46]。Iguchi等^[46]依据巢团内癌细胞计数及MVI数量将MVI分为低危型:存在MVI但无其他危险因素;高危型:MVI数量≥2个或巢团内癌细胞计数≥50个。Feng等^[42]将MVI区分为非侵袭性(游离型和粘连型)和侵袭性(侵袭型和突破型),并结合MVI数量将MVI分为:I型,非侵袭性MVI且数量<5个;II型,侵袭性MVI或数量>5个;III型:侵袭性MVI且数量>5个。但是,目前MVI分型均基于非客观指标,尚需要多中心大样本研究加以验证。

本共识推荐使用《原发性肝癌病理诊断指南》的MVI病理分级标准:M0级:未发现MVI;M1级:≤5个MVI,且发生于近癌旁肝组织区域(≤1 cm);M2级:>5个MVI,或MVI发生于远癌旁肝组织区域(>1 cm)^[10]。已有研究结果显示:按照该标准区分MVI可以更准确地评估早期肝癌患者的预后,M0级、M1级、M2级患者肝切除术后的中位总生存时间(overall survival, OS)分别为61.1、52.7、27.4个月($P<0.001$),中位无瘤生存时间(disease-free survival, DFS)分别为43.0、29.1、13.1个月($P<0.001$)^[20,47]。

推荐意见1:建议使用《原发性肝癌病理诊断指南》推荐的MVI病理分级标准:M0级:未发现MVI;M1级:≤5个MVI,且发生于近癌旁肝组织区域(≤1 cm);M2级:>5个MVI,或MVI发生于远癌旁肝组织区域(>1 cm)(证据等级:B;推荐级别:强烈推荐)。

(二)标本取材法

目前肝癌切除标本的常用取材方法有3点法、

7点法、13点法和肝癌影像-数字化大体病理(image-matching digital macro-slide, IDS)等(图1)。海军军医大学第三附属医院团队的研究结果显示:“7点法”对于MVI的诊断率与“13点”相当(47.1%比51.3%, $P=0.517$),均显著优于“3点法”的34.5%($P=0.048$)),但“7点法”较“13点法”更为简便和实用^[20]。

已有研究结果显示:为了提高MVI的检出率,癌旁组织取材点的个数不应固定不变,应与肿瘤长径和数目呈正相关,长径为1~3 cm、3~5 cm、>5 cm和多发肿瘤的癌旁组织内,取材数应至少达到4个、6个、8个和8个,但该建议仍需更多研究予以验证^[45]。IDS是指对整个肝癌切除标本进行切片固定,再进一步借助全切片扫描(whole slide imaging, WSI)技术获得优质的可视化数字图像,最后根据扫描仪相匹配的软件对图像进行分析和诊断,包括MVI在内的肝癌病理学特征。IDS相较于传统的“7点法”可以显著提高MVI的检出率^[48]。但是IDS对于设备要求高且读片工作量大,在目前人工智能诊断尚不成熟的情况下,其大范围应用受到限制^[49]。

推荐意见 2:推荐使用“7点法”对肝癌标本进行取材(证据等级:B;推荐级别:强推荐),有条件的医学中心可使用IDS(证据等级:C;推荐级别:强推荐)。

(三)临床分型

结合病理分型和临床特征的临床分型不仅能更准确地预测肝癌伴MVI的预后,也可以细化肝癌伴MVI的临床治疗。Zhang等^[50]将AFP、肿瘤包膜、肿瘤长径、HBeAg、乙型病毒性肝炎(以下简称乙肝)病毒脱氧核糖核酸(hepatitis B virus deoxyribonucleic acid, HBV-DNA)肿瘤个数和食管/胃底静脉曲张等变量构建为列线图,可将肝癌伴MVI患者进行临床预后分型。海军军医大学第三附属医院团队的研究结果显示:肝癌患者的预后与AFP、是否存在肝硬化、肿瘤个数、肿瘤长径、MVI个数及分布显著相关,用这些因素建立的列线图通过计算得分可将患者分为3型,此临床分型可以准确预测预后,

且仅有C型患者能从术后辅助性TACE治疗中获益^[51]。但上述临床分型的可推广性尚需进一步验证。

二、MVI预测

MVI是目前可指导肝癌复发防治的最重要的病理学特征。MVI诊断依赖于对术后切除标本的组织病理学检查,而非对术前穿刺活组织病理学检查。但术后病理学检查的结果具有滞后性,不利于将MVI信息用于指导术前和术中治疗决策,由此,凸显术前预测MVI的必要性和重要性。目前可用于预测MVI的因素包括临床特征^[52-54]、影像学特征^[55-56]、影像组^[57-59]、蛋白组^[60]和基因组^[61-62]等各种组学研究提供的MVI相关特征。将影像组学特征应用于MVI预测的报道较多,但此类研究均存在样本量较小、缺乏外部验证、纳入患者的标准不统一等问题。总体而言,目前利用单一因素预测MVI的准确性均不理想,尤其是特异性较差。此外,报道的结果仍需多中心大样本资料加以验证。

多因素联合较单一因素可提高MVI预测的准确性。Lei等^[63]提出了MVI预测模型-EHBH列线图法,该研究纳入1 004例早期肝癌患者,列线图模型包括肿瘤长径、肿瘤个数、肿瘤包膜、AFP水平、PLT计数、HBV-DNA水平和影像学典型增强特征等7个因素,在最佳临界值为200时受试者工作特征曲线下面积(area under the receiver operating characteristic curve, AUC)灵敏度和特异度分别为0.81, 73.5%和76.6%。Lee等^[64]报道用AFP水平、异常凝血酶原(des-gamma-carboxyprothrombin, DCP)水平、瘤周强化和瘤周低密度等4个因素联合预测<3 cm肝癌的MVI的发生概率,共纳入了2家医学中心377例患者,其AUC、灵敏度和特异度分别为0.87、65.2%和85.9%。四川大学华西医院团队报道纳入2 160例患者的MVI预测研究,结果显示:AFP水平、DCP水平、肿瘤长径、卫星结节、AST及AST/ALT比值联合预测MVI的AUC为0.80^[65]。Sun等^[66]比较了上述预测方法,结果显示:EHBH列线图在目前所有预测方法中稳定性与可靠性最佳。

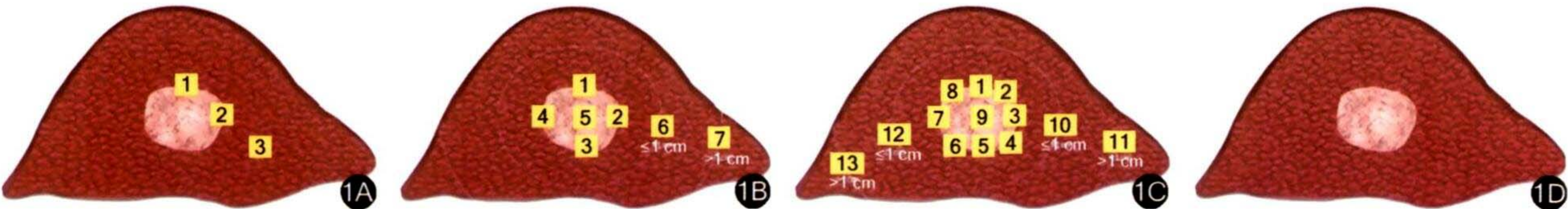


图1 常见的病理学检查标本取材方法 1A:3点法;1B:7点法;1C:13点法;1D:肝癌影像-数字化大体病理

Figure 1 Common pathological examination on specimen collection 1A: 3-points method; 1B: 7-points method; 1C: 13-points method; 1D: liver cancer imaging-image matching digital macro slide pathology

推荐意见 3: 建议肝癌患者术前进行 MVI 预测, 推荐使用 EHBH 列线图预测 MVI (证据等级: B; 推荐级别: 强推荐)。

三、MVI 指导治疗选择

肝癌伴 MVI 的治疗遵循保障安全性和改善肿瘤学预后 2 个主要原则。在保障治疗安全的前提下, 根据肿瘤情况和 MVI 信息, 首次治疗应选择对原发病灶及 MVI 根治性较佳的方法, 并强调多学科综合治疗, 以降低复发率, 延长生存时间, 改善生命质量。

(一) 首次根治性治疗

对于肝癌伴 MVI 的首次治疗, 比较不同治疗方法疗效的报道较少, 且缺乏前瞻性研究。已有研究结果显示: 术前预测为 MVI 高危的小肝癌 (长径 ≤ 3 cm) 患者, 肝切除术尤其是解剖性肝切除术 5 年 DFS 及 OS 显著优于经皮肝穿刺肝癌射频/微波消融术 (percutaneous radiofrequency ablation, PRFA/percutaneous microwave coagulation therapy, PMCT), 而低危患者的肝切除术与 PRFA/PMCT 疗效相似^[16,26,67-68]。对于符合米兰标准的肝癌患者, MVI 阳性患者的肝移植远期预后优于肝切除术, 而在阴性患者中解剖性肝切除术与肝移植的预后无显著性差异^[69-70]。但也有研究结果显示: 与肝切除术比较, 肝移植并不能使可切除肝癌伴 MVI 患者生存获益, 只能使 MVI 阴性患者获益^[71]。MVI 预测研究起步不久, 尚需更多临床试验充实其准确指导早期肝癌治疗决策的证据。

推荐意见 4: 对于肝癌可切除的患者建议首选手术切除 (证据等级: B; 推荐级别: 强推荐); 对于长径 ≤ 3 cm 且 MVI 预测为低危的患者可以选择手术或 PRFA/PMCT (证据等级: C; 推荐级别: 弱推荐)。

(二) 术后复发防治

1. 新辅助治疗

已有研究结果显示: 新辅助 TACE 导致的肿瘤坏死程度与术后病理学检查中的 MVI 检出率呈负相关^[72-73]。海军军医大学第三附属医院团队的研究结果显示: 在 TACE 后坏死面积 $>90\%$ 的肿瘤切除标本中, MVI 的检出率低于术前未行 TACE 的对照组 (8.1% 比 34.2%, $P < 0.05$), 坏死面积为 60%~90% 两组检出率相似 (47.1% 比 43.3%, $P > 0.05$), 坏死面积 $<60\%$ TACE 组的检出率显著高于对照组 (88.0% 比 48.0%, $P < 0.05$)^[73]; 总体而言, 肝切除术前新辅助 TACE 不能降低 MVI 总体发生率及改善预后^[73-74]。Kim 等^[75]对符合米兰标准的肝移植患者

给予新辅助 TACE, 结果显示: 该治疗不能降低 MVI 的发生率及改善远期生存。目前尚缺乏新辅助 TACE 对术前预测 MVI 高危患者的疗效报道。海军军医大学第三附属医院团队的 1 项随机对照研究结果显示: 术前放疗不能降低 MVI 高危者肝切除术后复发率和延长总体生存时间, 但该研究样本量较小, 其结果仍需大样本前瞻性研究验证^[76]。

推荐意见 5: 暂不建议对 MVI 预测高危肝癌患者单独使用 TACE 或放疗作为新辅助治疗 (证据等级: C; 推荐级别: 弱推荐); 为降低术后复发率, 鼓励在此类患者中开展新辅助治疗临床试验 (GPS)。

2. 术中治疗

解剖性肝切除术对病理 MVI 阳性肝癌患者的远期疗效优于非解剖性肝切除术^[26,77-89], 且腹腔镜肝切除术与开腹肝切除术的疗效相似^[90], 而 MVI 阴性患者则不能从解剖性肝切除术中获益^[83,87-88]。在肝切除术患者中, 除手术方式之外, 切缘的宽度也与预后密切相关。宽切缘 (切缘距离 ≥ 1 cm) 切除显著延长 MVI 阳性患者的 DFS 和 OS^[81,89,91-94]; 其预后价值甚至比解剖性肝切除术更重要^[95-99]; 但 MVI 阴性患者能否从宽切缘切除获益仍存在争议^[93-94,99-100]。此外, 1 项前瞻性 II 期临床试验报道术中放疗显著改善窄切缘的中央型伴 MVI 阳性肝癌患者的术后 DFS 及 OS, 但对 MVI 阴性患者无此作用。MVI 所致肿瘤肝内播散转移是患者死亡的主要原因^[101]。在保证手术安全的前提下, 术中宜减少、减轻对肝脏及肿瘤的挤压、翻转, 行原位切除可减少和避免肝内播散转移的风险。先行离断或阻断相应的流域血管也有利于减少此风险。

推荐意见 6: 建议对 MVI 预测高危肝癌患者行解剖性肝切除术或保证切缘距离 ≥ 1 cm (证据等级: B; 推荐级别: 强推荐); 如果不能行解剖性肝切除术或不能保证切缘距离 ≥ 1 cm, 有条件的医学中心可行术中放疗 (证据等级: C; 推荐级别: 弱推荐)。

3. 术后辅助治疗

肝癌伴 MVI 患者的术后辅助治疗主要包括以下措施:

(1) 抗病毒治疗。对于有乙肝背景的肝癌伴 MVI 患者, 规范化的抗病毒治疗既可保护肝功能, 又可降低复发率并改善远期生存。已有研究结果显示: 术前抗病毒治疗可显著降低 MVI 发生率^[102-104], 术后持续抗病毒治疗可显著延长 DFS 和 OS^[89,105-109]。目前常用的抗 HBV 核苷类似物/核苷酸类似物药物包括恩替卡韦、富马酸替诺福韦和丙酚替诺福

韦等。

(2)辅助性 TACE。TACE 是国内最常用的肝癌肝切除术后辅助治疗手段,治疗周期短且安全性较高。较多研究结果显示:TACE 降低肝癌伴 MVI 患者的复发率并延长生存时间^[89,110-114],但对 MVI 阴性者无此作用^[115-116]。已有研究结果显示:术后 2 次辅助性 TACE 的疗效优于 1 次,但该结果的可靠性仍需进一步证实^[117]。此外,东方肝胆 MVI 临床分型中仅有 C 型能从辅助性 TACE 获益,A 型和 B 型能否获益仍需进一步研究^[51]。

(3)辅助性放疗。2 项前瞻性研究结果均显示:肝切除术后辅助性放疗显著延长肝癌伴 MVI 患者的 DFS 及 OS^[118-119],对窄切缘者更具有优势。另有回顾性研究结果显示:术后辅助性放疗优于辅助性 TACE,但此方面的研究证据尚少^[120-121]。肝癌伴 MVI 的术后放疗技术推荐采用常规分割调强放射治疗,总剂量 50~60Gy,靶区建议包括手术切缘旁开 1.0~2.0 cm 的肝实质。

(4)辅助性肝动脉灌注化疗(hepatic arterial infusion chemotherapy, HAIC)。国内 1 项纳入 315 例肝癌伴 MVI 患者的多中心随机对照研究结果显示:基于 FOLFOX 化疗方案的术后辅助性 HAIC 较对照组显著降低复发率^[122]。另 1 项纳入 11 项研究共 1 290 例患者的荟萃分析结果显示:术后辅助性 HAIC 可使肝癌伴 MVI 亚组患者生存获益^[123]。

(5)术后靶向治疗或靶向联合免疫治疗。虽然 STORM 试验^[124]未能证实索拉非尼可降低肝癌术后复发,但其他文献报道术后索拉非尼^[125-127]或仑伐替尼^[128-129]可以使肝癌伴 MVI 者获益。阿替利珠单抗联合贝伐珠单抗联合免疫治疗(T+A)方案辅助治疗研究(IMbrave050 研究)中期分析已达到了 DFS 的主要终点,该治疗使高复发风险者的复发/远处转移或死亡风险下降 28%(DFS 的 HR=0.72),提示 T+A 方案可作为肝癌伴 MVI 患者的有效辅助治疗^[130]。海军军医大学第三附属医院 1 项纳入 198 例肝癌伴 MVI 患者的前瞻性随机对照研究已达预设终点^[131],与主动监测比较,信迪利单抗联合免疫治疗可显著延长 DFS(27.7 个月比 15.5 个月, $P<0.001$),但还需进一步随访以确认 OS 的差异。此外,尚有多项 II 期或 III 期的靶向免疫治疗预防肝癌术后复发的临床研究结果有待公布。在选择靶向免疫治疗前需评估患者的一般体力状态、肝功能状态和治疗风险等,基线评估及不良反应处理等建议参照中国医师协会肝癌专业委员会发布的《肝细胞癌免疫治疗中

国专家共识(2021)》^[132]及《肝细胞癌分子靶向药物临床应用中国专家共识(2022)》^[133]。

(6)术后局部治疗联合系统治疗。术后联合辅助治疗可能优于单一辅助治疗,例如 TACE 联合抗病毒治疗^[105]优于单用抗病毒治疗或 TACE, TACE 联合索拉非尼^[134]优于单用索拉非尼或 TACE 等,但上述均为回顾性研究,未来仍需更多证据加以明确。

(7)肝移植术后辅助治疗。对于 MVI 阳性肝癌行肝移植者,除常规的早期调整免疫抑制剂方案外,文献报道针对预防肝癌伴 MVI 移植后复发的治疗手段还包括系统化疗^[135]和血浆置换^[136]等,但仍需前瞻性研究进一步明确疗效。

推荐意见 7:建议对乙肝背景肝癌患者术后常规进行抗病毒治疗(证据等级:A;推荐级别:强推荐),对于术后病理学检查诊断 MVI 阳性患者还应依据实际情况推荐以下至少 1 种辅助治疗:T+A(证据等级:A;推荐级别:强推荐),信迪利单抗联合免疫治疗(证据等级:A;推荐级别:强推荐),TACE(证据等级:B;推荐级别:强推荐),放疗(证据等级:B;推荐级别:强推荐),HAIC(证据等级:A;推荐级别:强推荐),仑伐替尼或索拉非尼(证据等级:C;推荐级别:弱推荐)。

(三)复发后治疗

文献报道 MVI 阳性肝癌较 MVI 阴性肝癌有复发率高、易于肝外转移和进展快等特点^[137-142]。已有研究结果显示:MVI 阳性肝癌复发且处于 BCLC 0/A 期者,再切除和 RFA 的疗效优于 TACE,但 BCLC B/C 期者 3 种治疗的疗效相似^[143]。参考《肝细胞癌术后复发和转移的多学科管理:国际专家共识》^[144],结合共识委员会讨论意见,本共识建议:即使 MVI 阳性肝癌复发后预后较差,但如果符合 PRFA/PMCT 指征则首选该治疗;如果复发灶为单发、无门静脉主干癌栓且至复发时间(time to recurrence, TTR)≥1 年,可考虑手术切除。同时,复发灶行综合治疗的效果优于单一治疗,如前次 MVI 阳性的复发性小肝癌患者行 TACE 联合 RFA^[145-146]或索拉非尼联合 RFA^[147]的疗效优于单用 RFA;前次 MVI 阳性的复发性不可切除肝癌行 TACE 联合索拉非尼的效果优于单用 TACE^[148]等。因此, MVI 阳性肝癌复发后的治疗需谨慎对待,需结合肿瘤复发的位置、TTR、复发病灶的数量及分布等综合考虑,建议经多学科团队(multidisciplinary team, MDT)讨论后决定相应的治疗方案。

推荐意见 8:建议 MDT 讨论后决定 MVI 阳性

肝癌复发防治方案:复发灶 ≤ 3 个且最大肿瘤长径 ≤ 3 cm 则首选 PRFA/PMCT;如果复发灶为单发、无门静脉主干癌栓且 TTR ≥ 1 年,可考虑手术切除;对于复发灶不可切除,或早期复发(TTR ≤ 1 年)且无法行 PMCT/PRFA 的患者可行 TACE(证据等级:B;推荐级别:强推荐)。

四、多学科诊断与治疗流程

MDT 通过多学科协同诊断与治疗,最大程度发挥各学科的专业优势,让患者获益最大化,肝癌伴 MVI 的诊断与治疗更需要通过 MDT 制订诊断与治疗方

五、展望

近年来,肝癌伴 MVI 的诊断、预测和治疗取得了长足的进步,但仍有诸多问题亟需解决,例如:(1)预测 MVI 的准确性仍需提升,既往大量的文献已证实单一临床指标难以准确预测 MVI,将来引入组学数据等新变量可能提高预测准确性。(2)MVI 的病理学检查尚需不断完善,目前最常用的病理学检查标本取材“7 点法”对于 MVI 的检出率显著低于 IDS,但 IDS 的推广难度较大,因此,现阶段如何平衡取材、检出率和推广应用尚需进一步探索。(3)我国肝癌伴 MVI 患者数量众多,现有的共识推荐意见循证级别还较低,今后应充分利用我国的病例资源,结合最新的治疗进展如靶免治疗、双免治疗等,通过开展更多的随机对照研究以建立更为有效的肝癌伴 MVI 的治疗方法和方案。(4)肝癌发生 MVI 的分子机制研究尚需进一步研究,为治疗提供新靶点和新疗法。

《肝细胞癌伴微血管侵犯诊断和治疗中国专家共识(2024 版)》

编审委员会成员名单

顾问:

刘允怡 香港中文大学
郑树森 树兰(杭州)医院

陈孝平 华中科技大学同济医学院附属同济医院
董家鸿 清华大学附属北京清华长庚医院
樊 嘉 复旦大学附属中山医院
滕皋军 东南大学附属中大医院

主任委员:

沈 锋 海军军医大学第三附属医院
程树群 海军军医大学第三附属医院

副主任委员(按姓氏汉语拼音排序):

蔡建强 中国医学科学院肿瘤医院
陈敏山 中山大学肿瘤防治中心
戴朝六 中国医科大学附属盛京医院
方驰华 南方医科大学珠江医院
纪智礼 首都医科大学附属北京安贞医院
文天夫 四川大学华西医院
夏景林 温州医科大学附属第一医院
应敏刚 厦门弘爱医院
张志伟 华中科技大学同济医学院附属同济医院
张学文 吉林大学第二医院

委员(按姓氏汉语拼音排序):

毕新宇 中国医学科学院肿瘤医院
车 旭 中国医学科学院肿瘤医院
陈 钢 温州医科大学附属第一医院
程张军 东南大学附属中大医院
丛文铭 海军军医大学第三附属医院
单云峰 温州医科大学附属第一医院
董 辉 海军军医大学第三附属医院
范瑞芳 联勤保障部队第九四〇医院
冯 爽 海军军医大学第三附属医院
郭荣平 中山大学肿瘤防治中心
郭卫星 海军军医大学第三附属医院
华向东 中国医科大学肿瘤医院
蒺卫东 中国科学技术大学附属第一医院
贾宁阳 海军军医大学第三附属医院
靳 斌 山东大学齐鲁医院
李 滨 厦门大学附属第一医院
李广欣 清华大学附属北京清华长庚医院
李 靖 陆军军医大学新桥医院
李江涛 浙江大学医学院附属第二医院
李 秋 四川大学华西医院
李 巍 吉林大学中日联谊医院
刘恩宇 山东大学齐鲁医院
刘付宝 安徽医科大学第一附属医院
刘文松 上海市第六人民医院金山分院
麻 勇 哈尔滨医科大学附属第一医院
孟 岩 海军军医大学第三附属医院
彭 伟 四川大学华西医院
钱叶本 安徽医科大学第一附属医院
石 洁 海军军医大学第三附属医院

隋承军 海军军医大学第三附属医院
孙倍成 安徽医科大学第一附属医院
孙居仙 海军军医大学第三附属医院
孙志为 云南省第一人民医院
谭 广 大连医科大学附属第一医院
唐裕福 北部战区总医院
万 春 南阳市中心医院
王 康 海军军医大学第三附属医院
王 鲁 复旦大学附属肿瘤医院
魏文京 太原市人民医院
卫旭彪 海军军医大学第三附属医院
夏 勇 海军军医大学第三附属医院
向邦德 广西医科大学附属肿瘤医院
许 浏 嘉兴市第一医院
严茂林 福建省立医院
翟 健 海军军医大学第三附属医院
曾昭冲 复旦大学附属中山医院
张佳林 中国医科大学附属第一医院
张修平 中国人民解放军总医院
张 宇 四川省人民医院
张震生 海南省人民医院
章爱斌 浙江大学医学院附属第一医院
赵海涛 北京协和医院
周存才 江西省肿瘤医院
周鸿鲲 嘉兴市第一医院
周华邦 海军军医大学第三附属医院
周 俭 复旦大学附属中山医院
周进学 河南省肿瘤医院
周伟平 海军军医大学第三附属医院

执笔:

孙居仙 海军军医大学第三附属医院
夏 勇 海军军医大学第三附属医院
利益冲突 所有作者均声明不存在利益冲突

参 考 文 献

[1] Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics,2023 [J]. CA Cancer J Clin,2023,73(1):17-48. DOI:10.3322/caac.21763.

[2] Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma[J]. Semin Liver Dis,2005,25(2):181-200. DOI:10.1055/s-2005-871198.

[3] Tabrizian P, Jibara G, Shrager B, et al. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis[J]. Ann Surg,2015,261(5):947-955. DOI:10.1097/SLA.0000000000000710.

[4] Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis[J]. Lancet Oncol,2009,10(1): 35-43. DOI: 10.1016/S1470-2045(08)70284-5.

[5] Xu X, Lu D, Ling Q, et al. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria[J]. Gut,2016; 65(6):1035-1041. DOI:10.1136/gutjnl-2014-308513.

[6] Xu SL, Zhang YC, Wang GY, et al. Survival analysis of sirolimus-based immunosuppression in liver transplantation in patients with hepatocellular carcinoma[J]. Clin Res Hepatol Gastroenterol,2016,40(6):674-681. DOI:10.1016/j.clinre.2016.03.006.

[7] Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α -fetoprotein improves the performance of Milan criteria[J]. Gastroenterology,2012,143(4): 986-994. e3; quiz e14-e15. DOI:10.1053/j.gastro.2012.05.052.

[8] Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults[J]. Gut,2003,52 (Suppl 3):iii1-8. DOI:10.1136/gut.52.suppl_3.iii1.

[9] U.S. Preventive Services Task Force. Grade Definitions and suggestions for practice[EB/OL]. Available from: <http://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions,2012-10-12/2021-11-10>.

[10] Cong WM, Bu H, Chen J, et al. Practice guidelines for the pathological diagnosis of primary liver cancer: 2015 update[J]. World J Gastroenterol,2016,22(42):9279-9287. DOI:10.3748/wjg.v22.i42.9279.

[11] Altendorf-Hofmann A, Scheele J. [Indication and surgical outcome in hepatocellular carcinoma with infiltration of blood vessels, bile ducts and lymph nodes][J]. Kongressbd Dtsch Ges Chir Kongr,2002,119:635-641.

[12] Cucchetti A, Piscaglia F, Grigioni AD, et al. Preoperative prediction of hepatocellular carcinoma tumour grade and micro-vascular invasion by means of artificial neural network: a pilot study[J]. J Hepatol,2010,52(6):880-888. DOI: 10.1016/j.jhep.2009.12.037.

[13] Hung HH, Lei HJ, Chau GY, et al. Milan criteria, multi-nodularity, and microvascular invasion predict the recurrence patterns of hepatocellular carcinoma after resection[J]. J Gastrointest Surg,2013,17(4):702-711. DOI:10.1007/s11605-012-2087-z.

[14] Jun L, Zhenlin Y, Renyan G, et al. Independent factors and predictive score for extrahepatic metastasis of hepatocellular carcinoma following curative hepatectomy[J]. Oncologist, 2012,17(7):963-969. DOI:10.1634/theoncologist.2011-0447.

[15] Huang C, Zhu XD, Ji Y, et al. Microvascular invasion has limited clinical values in hepatocellular carcinoma patients at Barcelona Clinic Liver Cancer (BCLC) stages 0 or B[J]. BMC Cancer,2017,17(1):58. DOI:10.1186/s12885-017-3050-x.

[16] Imai K, Yamashita YI, Yusa T, et al. Microvascular invasion in small-sized hepatocellular carcinoma: significance for outcomes following hepatectomy and radiofrequency ablation[J]. Anticancer Res,2018, 38(2):1053-1060. DOI:10.21873/anticancer.12322.

[17] Li ZL, Yu JJ, Guo JW, et al. Liver resection is justified for multinodular hepatocellular carcinoma in selected patients with cirrhosis: a multicenter analysis of 1,066 patients[J]. Eur J Surg Oncol,2019,45(5):800-807. DOI:10.1016/j.ejso.2018.12.016.

[18] Shindoh J, Kobayashi Y, Kawamura Y, et al. Microvascular invasion and a size cutoff value of 2 cm predict long-term oncological outcome in multiple hepatocellular carcinoma: reappraisal of the American Joint Committee on Cancer Staging System and Validation Using the Surveillance, Epidemiology, and End-Results Database[J]. Liver Cancer,2020, 9(2):156-166. DOI:10.1159/000504193.

[19] Zhang XP, Zhou TF, Wang ZH, et al. Association of preoper-

- active hypercoagulability with poor prognosis in hepatocellular carcinoma patients with microvascular invasion after liver resection: a multicenter study[J]. *Ann Surg Oncol*, 2019,26(12):4117-4125. DOI:10.1245/s10434-019-07504-7.
- [20] Sheng X, Ji Y, Ren GP, et al. A standardized pathological proposal for evaluating microvascular invasion of hepatocellular carcinoma: a multicenter study by LCPGC[J]. *Hepatol Int*, 2020,14(6):1034-1047. DOI:10.1007/s12072-020-10111-4.
- [21] Liu H, Yang Y, Chen C, et al. Reclassification of tumor size for solitary HBV-related hepatocellular carcinoma by minimum p value method: a large retrospective study[J]. *World J Surg Oncol*, 2020,8(1):185. DOI:10.1186/s12957-020-01963-z.
- [22] Lee S, Kim SH, Lee JE, et al. Preoperative gadoxetic acid-enhanced MRI for predicting microvascular invasion in patients with single hepatocellular carcinoma[J]. *J Hepatol*, 2017,67(3):526-534. DOI:10.1016/j.jhep.2017.04.024.
- [23] Esnaola NF, Lauwers GY, Mirza NQ, et al. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation[J]. *J Gastrointest Surg*, 2002, 6(2):224-232. DOI: 10.1016/s1091-255x(01)00015-4.
- [24] Kim MJ, Lee M, Choi JY, et al. Imaging features of small hepatocellular carcinomas with microvascular invasion on gadoxetic acid-enhanced MR imaging[J]. *Eur J Radiol*, 2012, 81(10):2507-2512. DOI:10.1016/j.ejrad.2011.11.014.
- [25] Shindoh J, Andreou A, Aloia TA, et al. Microvascular invasion does not predict long-term survival in hepatocellular carcinoma up to 2 cm: reappraisal of the staging system for solitary tumors[J]. *Ann Surg Oncol*, 2013,20(4):1223-1229. DOI:10.1245/s10434-012-2739-y.
- [26] Yamashita YI, Imai K, Yusa T, et al. Microvascular invasion of single small hepatocellular carcinoma ≤ 3 cm: predictors and optimal treatments[J]. *Ann Gastroenterol Surg*, 2018,2(3):197-203. DOI:10.1002/ags3.12057.
- [27] Bhattacharjya S, Bhattacharjya T, Quaglia A, et al. Liver transplantation in cirrhotic patients with small hepatocellular carcinoma: an analysis of pre-operative imaging, explant histology and prognostic histologic indicators[J]. *Dig Surg*, 2004,21(2):152-160. DOI:10.1159/000078741.
- [28] Zhou JM, Zhou CY, Chen XP, et al. Anatomic resection improved the long-term outcome of hepatocellular carcinoma patients with microvascular invasion: a prospective cohort study[J]. *World J Gastrointest Oncol*, 2021,13(12):2190-2202. DOI:10.4251/wjgo.v13.i12.2190.
- [29] Löhe F, Angele MK, Rentsch M, et al. Multifocal manifestation does not affect vascular invasion of hepatocellular carcinoma: implications for patient selection in liver transplantation[J]. *Clin Transplant*, 2007,21(6):696-701. DOI:10.1111/j.1399-0012.2007.00707.x.
- [30] Nagano Y, Shimada H, Takeda K, et al. Predictive factors of microvascular invasion in patients with hepatocellular carcinoma larger than 5 cm[J]. *World J Surg*, 2008,32(10):2218-2222. DOI:10.1007/s00268-008-9585-x.
- [31] Kim JM, Kwon CH, Joh JW, et al. The effect of alkaline phosphatase and intrahepatic metastases in large hepatocellular carcinoma[J]. *World J Surg Oncol*, 2013,11:40. DOI:10.1186/1477-7819-11-40.
- [32] Lim C, Mise Y, Sakamoto Y, et al. Above 5 cm, size does not matter anymore in patients with hepatocellular carcinoma[J]. *World J Surg*, 2014,38(11):2910-2908. DOI: 10.1007/s00268-014-2704-y.
- [33] Kluger MD, Salceda JA, Laurent A, et al. Liver resection for hepatocellular carcinoma in 313 Western patients: tumor biology and underlying liver rather than tumor size drive prognosis[J]. *J Hepatol*, 2015,62(5):1131-1140. DOI:10.1016/j.jhep.2014.12.018.
- [34] Kim PT, Jang JH, Atenafu EG, et al. Outcomes after hepatic resection and subsequent multimodal treatment of recurrence for multifocal hepatocellular carcinoma[J]. *Br J Surg*, 2013, 100(11):1516-1522. DOI:10.1002/bjs.9263.
- [35] Wang BW, Mok KT, Liu SI, et al. Is hepatectomy beneficial in the treatment of multinodular hepatocellular carcinoma? [J]. *J Formos Med Assoc*, 2008,107(8):616-626. DOI:10.1016/S0929-6646(08)60179-5.
- [36] Goh BK, Chow PK, Teo JY, et al. Number of nodules, Child-Pugh status, margin positivity, and microvascular invasion, but not tumor size, are prognostic factors of survival after liver resection for multifocal hepatocellular carcinoma[J]. *J Gastrointest Surg*, 2014,18(8):1477-1485. DOI:10.1007/s11605-014-2542-0.
- [37] Wang H, Qian YW, Wu MC, et al. Liver resection is justified in patients with BCLC intermediate stage hepatocellular carcinoma without microvascular invasion[J]. *J Gastrointest Surg*, 2020,24(12):2737-2747. DOI:10.1007/s11605-019-04251-8.
- [38] Parfitt JR, Marotta P, Alghamdi M, et al. Recurrent hepatocellular carcinoma after transplantation: use of a pathological score on explanted livers to predict recurrence[J]. *Liver Transpl*, 2007,13(4):543-551. DOI:10.1002/lt.21078.
- [39] Zheng J, Chou JF, Gönen M, et al. Prediction of hepatocellular carcinoma recurrence beyond milan criteria after resection: validation of a clinical risk score in an international cohort[J]. *Ann Surg*, 2017,266(4):693-701. DOI: 10.1097/SLA.0000000000002360.
- [40] Hwang YJ, Bae JS, Lee Y, et al. Classification of microvascular invasion of hepatocellular carcinoma: correlation with prognosis and magnetic resonance imaging[J]. *Clin Mol Hepatol*, 2023,29(3):733-746. DOI:10.3350/cmh.2023.0034.
- [41] Sumie S, Nakashima O, Okuda K, et al. The significance of classifying microvascular invasion in patients with hepatocellular carcinoma[J]. *Ann Surg Oncol*, 2014,21(3):1002-1009. DOI:10.1245/s10434-013-3376-9.
- [42] Feng LH, Dong H, Lau WY, et al. Novel microvascular invasion-based prognostic nomograms to predict survival outcomes in patients after R0 resection for hepatocellular carcinoma[J]. *J Cancer Res Clin Oncol*, 2017,143(2):293-303. DOI:10.1007/s00432-016-2286-1.
- [43] Zhao H, Chen C, Fu X, et al. Prognostic value of a novel risk classification of microvascular invasion in patients with hepatocellular carcinoma after resection[J]. *Oncotarget*, 2017,8(3):5474-5486. DOI:10.18632/oncotarget.12547.
- [44] Roayaie S, Blume IN, Thung SN, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma[J]. *Gastroenterology*, 2009,137(3):850-855. DOI:10.1053/j.gastro.2009.06.003.
- [45] Chen L, Chen S, Zhou Q, et al. Microvascular invasion status and its survival impact in hepatocellular carcinoma depend on tissue sampling protocol[J]. *Ann Surg Oncol*, 2021,28(11):6747-6757. DOI:10.1245/s10434-021-09673-w.
- [46] Iguchi T, Shirabe K, Aishima S, et al. New pathologic stratification of microvascular invasion in hepatocellular carcinoma.

- noma: predicting prognosis after living-donor liver transplantation[J]. *Transplantation*, 2015, 99(6):1236-1242. DOI: 10.1097/TP.0000000000000489.
- [47] Xu XF, Diao YK, Zeng YY, et al. Association of severity in the grading of microvascular invasion with long-term oncological prognosis after liver resection for early-stage hepatocellular carcinoma: a multicenter retrospective cohort study from a hepatitis B virus-endemic area[J]. *Int J Surg*, 2023, 109(4):841-849. DOI: 10.1097/JS9.0000000000000325.
- [48] Yu HM, Wang K, Feng JK, et al. Image-matching digital macro-slide-a novel pathological examination method for microvascular invasion detection in hepatocellular carcinoma[J]. *Hepatol Int*, 2022, 16(2): 381-395. DOI: 10.1007/s12072-022-10307-w.
- [49] Sun L, Sun Z, Wang C, et al. PCformer: an MVI recognition method via classification of the MVI boundary according to histopathological images of liver cancer[J]. *J Opt Soc Am A Opt Image Sci Vis*, 2022, 39(9):1673-1681. DOI: 10.1364/JOSAA.463439.
- [50] Zhang XP, Wang K, Wei XB, et al. An eastern hepatobiliary surgery hospital microvascular invasion scoring system in predicting prognosis of patients with hepatocellular carcinoma and microvascular invasion after R0 liver resection: a large-scale, multicenter study[J]. *Oncologist*, 2019, 24(12): e1476-e1488. DOI: 10.1634/theoncologist.2018-0868.
- [51] Wang K, Xiang YJ, Yu HM, et al. A novel classification in predicting prognosis and guiding postoperative management after R0 liver resection for patients with hepatocellular carcinoma and microvascular invasion[J]. *Eur J Surg Oncol*, 2022, 48(6): 1348-1355. DOI: 10.1016/j.ejso.2021.12.466.
- [52] Zhou J, Zhang Z, Zhou H, et al. Preoperative circulating tumor cells to predict microvascular invasion and dynamical detection indicate the prognosis of hepatocellular carcinoma[J]. *BMC Cancer*, 2020, 20(1): 1047. DOI: 10.1186/s12885-020-07488-8.
- [53] Li H, Li T, Hu J, et al. A nomogram to predict microvascular invasion in early hepatocellular carcinoma[J]. *J Cancer Res Ther*, 2021, 17(3): 652-657. DOI: 10.4103/jcrt.JCRT_1714_20.
- [54] Wei J, Jiang H, Zeng M, et al. Prediction of microvascular invasion in hepatocellular carcinoma via deep learning: a multi-center and prospective validation study[J]. *Cancers (Basel)*, 2021, 13(10): 2368. DOI: 10.3390/cancers13102368.
- [55] Song L, Li J, Luo Y. The importance of a nonsmooth tumor margin and incomplete tumor capsule in predicting HCC microvascular invasion on preoperative imaging examination: a systematic review and meta-analysis[J]. *Clin Imaging*, 2021, 76: 77-82. DOI: 10.1016/j.clinimag.2020.11.057.
- [56] Hong SB, Choi SH, Kim SY, et al. MRI features for predicting microvascular invasion of hepatocellular carcinoma: a systematic review and meta-analysis[J]. *Liver Cancer*, 2021, 10(2): 94-106. DOI: 10.1159/000513704.
- [57] Xu X, Zhang HL, Liu QP, et al. Radiomic analysis of contrast-enhanced CT predicts microvascular invasion and outcome in hepatocellular carcinoma[J]. *J Hepatol*, 2019, 70(6): 1133-1144. DOI: 10.1016/j.jhep.2019.02.023.
- [58] Zhang K, Zhang L, Li WC, et al. Radiomics nomogram for the prediction of microvascular invasion of HCC and patients' benefit from postoperative adjuvant TACE: a multicenter study[J]. *Eur Radiol*, 2023, 33(12): 8936-8947. DOI: 10.1007/s00330-023-09824-5.
- [59] Xiao Q, Zhu W, Tang H, et al. Ultrasound radiomics in the prediction of microvascular invasion in hepatocellular carcinoma: a systematic review and meta-analysis[J]. *Heliyon*, 2023, 9(6): e16997. DOI: 10.1016/j.heliyon.2023.e16997.
- [60] Wang Z, Cao L, Wang J, et al. A novel predictive model of microvascular invasion in hepatocellular carcinoma based on differential protein expression[J]. *BMC Gastroenterol*, 2023, 23(1): 89. DOI: 10.1186/s12876-023-02729-z.
- [61] Banerjee S, Wang DS, Kim HJ, et al. A computed tomography radiogenomic biomarker predicts microvascular invasion and clinical outcomes in hepatocellular carcinoma[J]. *Hepatology*, 2015, 62(3): 792-800. DOI: 10.1002/hep.27877.
- [62] Xin Z, Li J, Zhang H, et al. Cancer genomic alterations can be potential biomarkers predicting microvascular invasion and early recurrence of hepatocellular carcinoma[J]. *Front Oncol*, 2022, 12: 783109. DOI: 10.3389/fonc.2022.783109.
- [63] Lei Z, Li J, Wu D, et al. Nomogram for preoperative estimation of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma within the milan criteria [J]. *JAMA Surg*, 2016, 151(4): 356-363. DOI: 10.1001/jama surg.2015.4257.
- [64] Lee S, Kang TW, Song KD, et al. Effect of microvascular invasion risk on early recurrence of hepatocellular carcinoma after surgery and radiofrequency ablation[J]. *Ann Surg*, 2021, 273(3): 564-571. DOI: 10.1097/SLA.00000000000003268.
- [65] Liu W, Zhang L, Xin Z, et al. A Promising preoperative prediction model for microvascular invasion in hepatocellular carcinoma based on an extreme gradient boosting algorithm[J]. *Front Oncol*, 2022, 12: 852736. DOI: 10.3389/fonc.2022.852736.
- [66] Sun SW, Liu QP, Xu X, et al. Direct comparison of four pre-surgical stratifying schemes for prediction of microvascular invasion in hepatocellular carcinoma by gadoxetic acid-enhanced MRI[J]. *J Magn Reson Imaging*, 2020, 52(2): 433-447. DOI: 10.1002/jmri.27043.
- [67] Bai S, Yang P, Xie Z, et al. Preoperative estimated risk of microvascular invasion is associated with prognostic differences following liver resection versus radiofrequency ablation for early hepatitis b virus-related hepatocellular carcinoma[J]. *Ann Surg Oncol*, 2021, 28(13): 8174-8185. DOI: 10.1245/s10434-021-09901-3.
- [68] Imai K, Yamashita YI, Yusa T, et al. Microvascular invasion in small-sized hepatocellular carcinoma: significance for outcomes following hepatectomy and radiofrequency ablation[J]. *Anticancer Res*, 2018, 38(2): 1053-1060. DOI: 10.21873/anticancer.12322.
- [69] Yang P, Teng F, Bai S, et al. Liver resection versus liver transplantation for hepatocellular carcinoma within the Milan criteria based on estimated microvascular invasion risks [J]. *Gastroenterol Rep (Oxf)*, 2023, 11: goad035. DOI: 10.1093/gastro/goad035.
- [70] Chan SC, Fan ST, Chok KS, et al. Survival advantage of primary liver transplantation for hepatocellular carcinoma within the up-to-7 criteria with microvascular invasion[J]. *Hepatol Int*, 2012, 6(3): 646-656. DOI: 10.1007/s12072-011-9318-3.
- [71] Vitale A, Huo TL, Cucchetti A, et al. Survival benefit of liver transplantation versus resection for hepatocellular carcinoma: impact of meld score[J]. *Ann Surg Oncol*, 2015, 22(6): 1901-1907. DOI: 10.1245/s10434-014-4099-2.

- [72] Jeong J, Park JG, Seo KI, et al. Microvascular invasion may be the determining factor in selecting TACE as the initial treatment in patients with hepatocellular carcinoma[J]. *Medicine (Baltimore)*, 2021, 100(27):e26584. DOI:10.1097/MD.00000000000026584.
- [73] Yang Y, Dang Z, Lu P, et al. Impact of pathological response after preoperative transcatheter arterial chemoembolization (TACE) on incidences of microvascular invasion and early tumor recurrence in hepatocellular carcinoma: a multi-center propensity score matching analysis[J]. *Hepatobiliary Surg Nutr*, 2022, 11(3): 386-399. DOI: 10.21037/hbsn-20-700.
- [74] Yang Y, Lin K, Liu L, et al. Impact of preoperative TACE on incidences of microvascular invasion and long-term post-hepatectomy survival in hepatocellular carcinoma patients: a propensity score matching analysis[J]. *Cancer Med*, 2021, 10(6):2100-2111. DOI:10.1002/cam4.3814.
- [75] Kim JM, Kwon CH, Joh JW, et al. Effectiveness of locoregional therapy before living donor liver transplantation in patients with hepatocellular carcinoma who meet the Milan criteria[J]. *Transplant Proc*, 2012, 44(2): 403-408. DOI: 10.1016/j.transproceed.2012.01.067.
- [76] Wei X, Jiang Y, Feng S, et al. Neoadjuvant intensity modulated radiotherapy for a single and small (≤ 5 cm) hepatitis B virus-related hepatocellular carcinoma predicted to have high risks of microvascular invasion: a randomized clinical trial[J]. *Int J Surg*, 2023, 109(10):3052-3060. DOI: 10.1097/JS9.0000000000000574.
- [77] Zheng J, Wang N, Yuan J, et al. The appropriate method of hepatectomy for hepatocellular carcinoma within University of California San Francisco (UCSF) criteria through neural network analysis[J]. *HPB (Oxford)*, 2023, 25(5):497-506. DOI:10.1016/j.hpb.2023.02.001.
- [78] Hirose Y, Sakata J, Takizawa K, et al. Impact of anatomic resection on long-term survival in patients with hepatocellular carcinoma with T1-T2 disease or microscopic vascular invasion[J]. *Surg Oncol*, 2023, 49: 101951. DOI: 10.1016/j.suronc.2023.101951.
- [79] Meng XP, Tang TY, Ding ZM, et al. Preoperative microvascular invasion prediction to assist in surgical plan for single hepatocellular carcinoma: better together with radiomics[J]. *Ann Surg Oncol*, 2022, 29(5): 2960-2970. DOI: 10.1245/s10434-022-11346-1.
- [80] Hu H, Qi S, Zeng S, et al. Importance of microvascular invasion risk and tumor size on recurrence and survival of hepatocellular carcinoma after anatomical resection and non-anatomical resection[J]. *Front Oncol*, 2021, 11:621622. DOI:10.3389/fonc.2021.621622.
- [81] Shi C, Zhao Q, Liao B, et al. Anatomic resection and wide resection margin play an important role in hepatectomy for hepatocellular carcinoma with peritumoural micrometastasis[J]. *ANZ J Surg*, 2019, 89(11):E482-E486. DOI:10.1111/ans.15396.
- [82] Zhong XP, Zhang YF, Mei J, et al. Anatomical versus non-anatomical resection for hepatocellular carcinoma with microscope vascular invasion: a propensity score matching analysis[J]. *J Cancer*, 2019, 10(17):3950-3957. DOI: 10.7150/jca.32592.
- [83] Lin S, Ye F, Rong W, et al. Nomogram to assist in surgical plan for hepatocellular carcinoma: a prediction model for microvascular invasion[J]. *J Gastrointest Surg*, 2019, 23(12): 2372-2382. DOI:10.1007/s11605-019-04140-0.
- [84] Liu J, Zhu Q, Li Y, et al. Microvascular invasion and positive HB e antigen are associated with poorer survival after hepatectomy of early hepatocellular carcinoma: a retrospective cohort study[J]. *Clin Res Hepatol Gastroenterol*, 2018, 42(4):330-338. DOI:10.1016/j.clinre.2018.02.003.
- [85] Yamashita YI, Imai K, Yusa T, et al. Microvascular invasion of single small hepatocellular carcinoma ≤ 3 cm: predictors and optimal treatments[J]. *Ann Gastroenterol Surg*, 2018, 2(3):197-203. DOI:10.1002/ags3.12057.
- [86] Zhao H, Hua Y, Lu Z, et al. Prognostic value and preoperative predictors of microvascular invasion in solitary hepatocellular carcinoma ≤ 5 cm without macrovascular invasion[J]. *Oncotarget*, 2017, 8(37):61203-61214. DOI:10.18632/oncotarget.18049.
- [87] Cucchetti A, Qiao GL, Cescon M, et al. Anatomic versus non-anatomic resection in cirrhotic patients with early hepatocellular carcinoma[J]. *Surgery*, 2014, 155(3):512-521. DOI: 10.1016/j.surg.2013.10.009.
- [88] Fan LF, Zhao WC, Yang N, et al. Alpha-fetoprotein: the predictor of microvascular invasion in solitary small hepatocellular carcinoma and criterion for anatomic or non-anatomic hepatic resection[J]. *Hepatogastroenterology*, 2013, 60(124):825-836. DOI:10.5754/hge121039.
- [89] Chen ZH, Zhang XP, Feng JK, et al. Actual long-term survival in hepatocellular carcinoma patients with microvascular invasion: a multicenter study from China[J]. *Hepatol Int*, 2021, 15(3):642-650. DOI:10.1007/s12072-021-10174-x.
- [90] Yang SY, Yan ML, Duan YF, et al. Perioperative and long-term survival outcomes of laparoscopic versus laparotomic hepatectomy for BCLC stages 0-A hepatocellular carcinoma patients associated with or without microvascular invasion: a multicenter, propensity score matching analysis[J]. *Hepatol Int*, 2022, 16(4):892-905. DOI: 10.1007/s12072-022-10353-4.
- [91] Wang J, Wang W, Wang H, et al. Physiological and pathological functions of SLC26A6[J]. *Front Med (Lausanne)*, 2020, 7:618256. DOI:10.3389/fmed.2020.618256.
- [92] Han J, Li ZL, Xing H, et al. The impact of resection margin and microvascular invasion on long-term prognosis after curative resection of hepatocellular carcinoma: a multi-institutional study[J]. *HPB (Oxford)*, 2019, 21(8):962-971. DOI:10.1016/j.hpb.2018.11.005.
- [93] Yang P, Si A, Yang J, et al. A wide-margin liver resection improves long-term outcomes for patients with HBV-related hepatocellular carcinoma with microvascular invasion[J]. *Surgery*, 2019, 165(4):721-730. DOI: 10.1016/j.surg.2018.09.016.
- [94] Liu M, Wang L, Zhu H, et al. A preoperative measurement of serum microRNA-125b may predict the presence of microvascular invasion in hepatocellular carcinomas patients[J]. *Transl Oncol*, 2016, 9(3):167-172. DOI:10.1016/j.tranon.2016.03.002.
- [95] Liu J, Zhuang G, Bai S, et al. The comparison of surgical margins and type of hepatic resection for hepatocellular carcinoma with microvascular invasion[J]. *Oncologist*, 2023, 28(11):e1043-e1051. DOI:10.1093/oncolo/oyad124.
- [96] Zhang XP, Xu S, Lin ZY, et al. Significance of anatomical resection and resection margin status in patients with HBV-related hepatocellular carcinoma and microvascular invasion: a multicenter propensity score-matched study[J]. *Int J Surg*, 2023, 109(4):679-688. DOI: 10.1097/JS9.0000000000000204.

- [97] Zhou JM, Zhou CY, Chen XP, et al. Anatomic resection improved the long-term outcome of hepatocellular carcinoma patients with microvascular invasion: a prospective cohort study[J]. *World J Gastrointest Oncol*, 2021, 13(12):2190-2202. DOI:10.4251/wjgo.v13.i12.2190.
- [98] Shi F, Zhou Z, Huang X, et al. Is anatomical resection necessary for early hepatocellular carcinoma? A single institution retrospective experience[J]. *Future Oncol*, 2019, 15(17):2041-2051. DOI:10.2217/fon-2019-0117.
- [99] Shin S, Kim TS, Lee JW, et al. Is the anatomical resection necessary for single hepatocellular carcinoma smaller than 3 cm?: single-center experience of liver resection for a small HCC[J]. *Ann Hepatobiliary Pancreat Surg*, 2018, 22(4):326-334. DOI:10.14701/ahbps.2018.22.4.326.
- [100] Zhou Q, Zhou C, Yin Y, et al. Development and validation of a nomogram combining hematological and imaging features for preoperative prediction of microvascular invasion in hepatocellular carcinoma patients[J]. *Ann Transl Med*, 2021, 9(5):402. DOI:10.21037/atm-20-4695.
- [101] Wang L, Liu Y, Rong W, et al. The role of intraoperative electron radiotherapy in centrally located hepatocellular carcinomas treated with narrow-margin (<1 cm) hepatectomy: a prospective, phase 2 study[J]. *Hepatobiliary Surg Nutr*, 2022, 11(4):515-529. DOI:10.21037/hbsn-21-223.
- [102] Wang Z, Duan Y, Zhang J, et al. Preoperative antiviral therapy and microvascular invasion in hepatitis B virus-related hepatocellular carcinoma: a meta-analysis[J]. *Eur J Pharmacol*, 2020, 883:173382. DOI:10.1016/j.ejphar.2020.173382.
- [103] Qu C, Huang X, Liu K, et al. Effect of hepatitis B virus DNA replication level and anti-HBV therapy on microvascular invasion of hepatocellular carcinoma[J]. *Infect Agent Cancer*, 2019, 14:2. DOI:10.1186/s13027-019-0219-8.
- [104] Liu K, Duan J, Liu H, et al. Precancer antiviral treatment reduces microvascular invasion of early-stage hepatitis B-related hepatocellular carcinoma[J]. *Sci Rep*, 2019, 9(1):2220. DOI:10.1038/s41598-019-39440-7.
- [105] Tang Y, Zhang J, Chen G, et al. Efficacy of adjuvant transarterial chemoembolization combined antiviral therapy for hbv-related hcc with mvi after hepatic resection: a multicenter study[J]. *Asian Pac J Cancer Prev*, 2022, 23(8):2695-2703. DOI:10.31557/APJCP.2022.23.8.2695.
- [106] Kong J, Liang X, Zhang J, et al. Antiviral therapy improves survival in hepatocellular carcinoma with microvascular invasion: a propensity score analysis[J]. *Dig Dis Sci*, 2022, 67(8):4250-4257. DOI:10.1007/s10620-021-07248-z.
- [107] Li L, Li B, Zhang M. HBV DNA levels impact the prognosis of hepatocellular carcinoma patients with microvascular invasion[J]. *Medicine (Baltimore)*, 2019, 98(27):e16308. DOI:10.1097/MD.00000000000016308.
- [108] Wang Z, Duan Y, Zhang J, et al. Preoperative antiviral therapy and microvascular invasion in hepatitis B virus-related hepatocellular carcinoma: a meta-analysis[J]. *Eur J Pharmacol*, 2020, 883:173382. DOI:10.1016/j.ejphar.2020.173382.
- [109] Li Z, Lei Z, Xia Y, et al. Association of preoperative antiviral treatment with incidences of microvascular invasion and early tumor recurrence in hepatitis b virus-related hepatocellular carcinoma[J]. *JAMA Surg*, 2018, 153(10):e182721. DOI:10.1001/jamasurg.2018.2721.
- [110] Sun JJ, Wang K, Zhang CZ, et al. Postoperative adjuvant transcatheter arterial chemoembolization after R0 hepatectomy improves outcomes of patients who have hepatocellular carcinoma with microvascular invasion[J]. *Ann Surg Oncol*, 2016, 23(4):1344-1351. DOI:10.1245/s10434-015-5008-z.
- [111] Wei W, Jian PE, Li SH, et al. Adjuvant transcatheter arterial chemoembolization after curative resection for hepatocellular carcinoma patients with solitary tumor and microvascular invasion: a randomized clinical trial of efficacy and safety[J]. *Cancer Commun (Lond)*, 2018, 38(1):61. DOI:10.1186/s40880-018-0331-y.
- [112] Mo A, Lin B, Chen D. Efficacy of sequential TACE on primary hepatocellular carcinoma with microvascular invasion after radical resection: a systematic review and meta-analysis[J]. *World J Surg Oncol*, 2023, 21(1):277. DOI:10.1186/s12957-023-03160-0.
- [113] Liu ZH, Chai ZT, Feng JK, et al. A reasonable identification of the early recurrence time based on microvascular invasion for hepatocellular carcinoma after R0 resection: a multicenter retrospective study[J]. *Cancer Med*, 2023, 12(9):10294-10302. DOI:10.1002/cam4.5758.
- [114] Chen ZH, Zhang XP, Zhou TF, et al. Adjuvant transarterial chemoembolization improves survival outcomes in hepatocellular carcinoma with microvascular invasion: a systematic review and meta-analysis[J]. *Eur J Surg Oncol*, 2019, 45(11):2188-2196. DOI:10.1016/j.ejso.2019.06.031.
- [115] Ye JZ, Chen JZ, Li ZH, et al. Efficacy of postoperative adjuvant transcatheter arterial chemoembolization in hepatocellular carcinoma patients with microvascular invasion [J]. *World J Gastroenterol*, 2017, 23(41):7415-7424. DOI:10.3748/wjg.v23.i41.7415.
- [116] Luo L, Shan R, Cui L, et al. Postoperative adjuvant transarterial chemoembolisation improves survival of hepatocellular carcinoma patients with microvascular invasion: a multicenter retrospective cohort[J]. *United European Gastroenterol J*, 2023, 11(2):228-241. DOI:10.1002/ueg2.12365.
- [117] Gao Z, Du G, Pang Y, et al. Adjuvant transarterial chemoembolization after radical resection contributed to the outcomes of hepatocellular carcinoma patients with high-risk factors. *Medicine (Baltimore)* [J]. 2017, 96(33):e7426. DOI:10.1097/MD.00000000000007426.
- [118] Shi C, Li Y, Geng L, et al. Adjuvant stereotactic body radiotherapy after marginal resection for hepatocellular carcinoma with microvascular invasion: a randomised controlled trial[J]. *Eur J Cancer*, 2022, 166:176-184. DOI:10.1016/j.ejca.2022.02.012.
- [119] Wang L, Wang W, Rong W, et al. Postoperative adjuvant treatment strategy for hepatocellular carcinoma with microvascular invasion: a non-randomized interventional clinical study[J]. *BMC Cancer*, 2020, 20(1):614. DOI:10.1186/s12885-020-07087-7.
- [120] Wang L, Wang W, Yao X, et al. Postoperative adjuvant radiotherapy is associated with improved survival in hepatocellular carcinoma with microvascular invasion[J]. *Oncotarget*, 2017, 8(45):79971-79981. DOI:10.18632/oncotarget.20402.
- [121] Wang L, Chen B, Li Z, et al. Optimal postoperative adjuvant treatment strategy for HBV-related hepatocellular carcinoma with microvascular invasion: a propensity score analysis[J]. *Onco Targets Ther*, 2019, 12:1237-1247. DOI:10.2147/OTT.S179247.
- [122] Li SH, Mei J, Cheng Y, et al. Postoperative adjuvant hepatic arterial infusion chemotherapy with folfox in hepatocellular carcinoma with microvascular invasion: a multicenter, phase III, randomized study[J]. *J Clin Oncol*, 2023, 41(10):1898-1908. DOI:10.1200/JCO.22.01142.

- [123] Hu L, Zheng Y, Lin J, et al. Does adjuvant hepatic artery infusion chemotherapy improve patient outcomes for hepatocellular carcinoma following liver resection? A meta-analysis[J]. *World J Surg Oncol*, 2023, 21(1):121. DOI:10.1186/s12957-023-03000-1.
- [124] Pinyol R, Montal R, Bassaganyas L, et al. Molecular predictors of prevention of recurrence in HCC with sorafenib as adjuvant treatment and prognostic factors in the phase 3 STORM trial[J]. *Gut*, 2019, 68(6):1065-1075. DOI:10.1136/gutjnl-2018-316408.
- [125] Huang Y, Zhang Z, Zhou Y, et al. Should we apply sorafenib in hepatocellular carcinoma patients with microvascular invasion after curative hepatectomy? [J]. *Onco Targets Ther*, 2019, 12:541-548. DOI:10.2147/OTT.S187357.
- [126] Zhang XP, Chai ZT, Gao YZ, et al. Postoperative adjuvant sorafenib improves survival outcomes in hepatocellular carcinoma patients with microvascular invasion after R0 liver resection: a propensity score matching analysis[J]. *HPB (Oxford)*, 2019, 21(12):1687-1696. DOI:10.1016/j.hpb.2019.04.014.
- [127] Gu W, Tong Z. Sorafenib in the treatment of patients with hepatocellular carcinoma (HCC) and microvascular infiltration: a systematic review and meta-analysis[J]. *J Int Med Res*, 2020, 48(8):300060520946872. DOI: 10.1177/0300060520946872.
- [128] Bai S, Hu L, Liu J, et al. Prognostic nomograms combined adjuvant lenvatinib for hepatitis B virus-related hepatocellular carcinoma with microvascular invasion after radical resection[J]. *Front Oncol*, 2022, 12:919824. DOI: 10.3389/fonc.2022.919824.
- [129] Dai MG, Liu SY, Lu WF, et al. Survival benefits from adjuvant lenvatinib for patients with hepatocellular carcinoma and microvascular invasion after curative hepatectomy[J]. *Clin Med Insights Oncol*, 2023, 17:11795549231180351. DOI:10.1177/11795549231180351.
- [130] Qin S, Chen M, Cheng AL, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial[J]. *Lancet*, 2023, 402(10415):1835-1847. DOI:10.1016/S0140-6736(23)01796-8.
- [131] Wang K, Xiang YJ, Yu HM, et al. Adjuvant sintilimab in resected high-risk hepatocellular carcinoma: a randomized, controlled, phase 2 trial[J]. *Nat Med*, 2024[2024-01-25]. <https://pubmed.ncbi.nlm.nih.gov/38242982/>. DOI: 10.1038/s41591-023-02786-7. [Published ahead of print].
- [132] Yang Y, Sun J, Wu M, et al. Chinese expert consensus on immunotherapy for hepatocellular carcinoma (2021 edition) [J]. *Liver Cancer*, 2022, 11(6):511-526. DOI:10.1159/000526038.
- [133] 中国医师协会肝癌专业委员会. 肝细胞癌分子靶向药物临床应用中国专家共识(2020版)[J]. *中华医学杂志*, 2021, 101(28):2185-2194. DOI:10.3760/cma.j.cn112137-20210329-00760.
- [134] Feng W, Cao W, Cui C, et al. Efficacy of lipid nanoparticle-loaded sorafenib combined with hepatic artery chemoembolization in the treatment of primary hepatocellular carcinoma complicated with microvascular invasion[J]. *Dis Markers*, 2022, 2022:4996471. DOI:10.1155/2022/4996471.
- [135] Wu J, Sun H, Han Z, et al. A single center experience: post-transplantation adjuvant chemotherapy impacts the prognosis of hepatocellular carcinoma patients[J]. *Chin Med J (Engl)*, 2014, 127(3):430-434.
- [136] Oh N, Rhu J, Kim JM, et al. Improved recurrence-free survival in patients with HCC with post-transplant plasma exchange[J]. *Liver Transpl*, 2023, 29(8):804-812. DOI: 10.1097/LVT.000000000000147.
- [137] Kow AW, Kwon CH, Song S, et al. Risk factors of peritoneal recurrence and outcome of resected peritoneal recurrence after liver resection in hepatocellular carcinoma: review of 1222 cases of hepatectomy in a tertiary institution[J]. *Ann Surg Oncol*, 2012, 19(7):2246-2255. DOI:10.1245/s10434-012-2260-3.
- [138] Li J, Liu Y, Yan Z, et al. A nomogram predicting pulmonary metastasis of hepatocellular carcinoma following partial hepatectomy[J]. *Br J Cancer*, 2014, 110(5):1110-1117. DOI: 10.1038/bjc.2014.19.
- [139] Ali MA, Li WF, Wang JH, et al. Impact of pathological features of primary hepatocellular carcinoma on the outcomes of intrahepatic recurrence management: single center experience from Southern Taiwan[J]. *HPB (Oxford)*, 2016, 18(10):851-860. DOI:10.1016/j.hpb.2016.07.004.
- [140] Ryu T, Takami Y, Wada Y, et al. Efficacy of surgical microwave ablation for recurrent hepatocellular carcinoma after curative hepatectomy[J]. *HPB (Oxford)*, 2020, 22(3):461-469. DOI:10.1016/j.hpb.2019.08.001.
- [141] Chen SL, Xiao H, Xie ZL, et al. The presence of microvascular invasion guides treatment strategy in recurrent HBV-related HCC[J]. *Eur Radiol*, 2020, 30(6):3473-3485. DOI: 10.1007/s00330-019-06640-8.
- [142] Jin YJ, Lee JW, Lee OH, et al. Transarterial chemoembolization versus surgery/radiofrequency ablation for recurrent hepatocellular carcinoma with or without microvascular invasion[J]. *J Gastroenterol Hepatol*, 2014, 29(5):1056-1064. DOI:10.1111/jgh.12507.
- [143] Xiao H, Chen ZB, Jin HL, et al. Treatment selection of recurrent hepatocellular carcinoma with microvascular invasion at the initial hepatectomy[J]. *Am J Transl Res*, 2019, 11(3):1864-1875.
- [144] Wen T, Jin C, Facciorusso A, et al. Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: an international expert consensus [J]. *Hepatobiliary Surg Nutr*, 2018, 7(5):353-371. DOI: 10.21037/hbsn.2018.08.01.
- [145] Peng Z, Wu X, Li J, et al. The role of neoadjuvant conventional transarterial chemoembolization with radiofrequency ablation in the treatment of recurrent hepatocellular carcinoma after initial hepatectomy with microvascular invasion[J]. *Int J Hyperthermia*, 2022, 39(1):688-696. DOI: 10.1080/02656736.2022.2051613.
- [146] Sun X, Yang Z, Mei J, et al. The guiding value of microvascular invasion for treating early recurrent small hepatocellular carcinoma[J]. *Int J Hyperthermia*, 2021, 38(1):931-938. DOI:10.1080/02656736.2021.1937715.
- [147] Wei MC, Zhang YJ, Chen MS, et al. Adjuvant sorafenib following radiofrequency ablation for early-stage recurrent hepatocellular carcinoma with microvascular invasion at the initial hepatectomy[J]. *Front Oncol*, 2022, 12:868429. DOI:10.3389/fonc.2022.868429.
- [148] Peng Z, Chen S, Xiao H, et al. Microvascular invasion as a predictor of response to treatment with sorafenib and transarterial chemoembolization for recurrent intermediate-stage hepatocellular carcinoma[J]. *Radiology*, 2019, 292(1):237-247. DOI:10.1148/radiol.2019181818.