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肝细胞癌合并门静脉癌栓治疗进展

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摘　要

肝细胞癌(HCC)恶性程度高，进展快，是全球第四大癌症相关死亡原因。肝脏血供丰富，肝细胞癌在发生发展过程中极易侵犯血管，根据既往文献报道，侵犯门静脉系统并形成门静脉癌栓(PVTT)发生率在10%~60%。PVTT是肝癌预后的负面预测因素，一旦出现PVTT，常预示着肿瘤发生肝内播散和肝外转移，极易导致门静脉高压相关并发症。仅接受支持治疗时，患者的总生存期(OS)仅为2至4个月。伴有PVTT的HCC治疗方式选择有限，国内外指南推荐仍存在争议。近年来，随着TACE、放疗、系统治疗等综合治疗手段的新兴和发展，不同治疗方式均显示出了一定的疗效。本文拟对肝细胞癌合并门静脉癌栓治疗进展作一综述。

关键词

肝细胞癌，门静脉癌栓，综合治疗，转化治疗，局部治疗

Progress in Treatment of Hepatocellular Carcinoma Combined with Portal Vein Cancer Thrombus

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Abstract

Hepatocellular carcinoma (HCC) is highly malignant and progresses rapidly, making it the fourth

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leading cause of cancer-related death worldwide. The liver has a rich blood supply, and HCC readily invades blood vessels during its development and progression. Previous studies have reported that invasion of the portal venous system with the formation of portal vein tumor thrombus (PVTT) occurs in 10%~60% of cases. PVTT is a negative prognostic factor for HCC. Once PVTT develops, it often indicates intrahepatic dissemination and extrahepatic metastasis of the tumor, and it can readily lead to complications related to portal hypertension. With supportive care alone, the overall survival (OS) of patients is only 2 to 4 months. Treatment options for HCC with PVTT are limited, and recommendations in domestic and international guidelines remain controversial. In recent years, with the emergence and development of multimodal treatment strategies such as transarterial chemoembolization (TACE), radiotherapy, and systemic therapy, various treatment modalities have demonstrated certain therapeutic efficacy. This article aims to review advances in the treatment of hepatocellular carcinoma complicated by portal vein tumor thrombus.

Keywords

Hepatocellular Carcinoma, Portal Vein Cancer Thrombus, Comprehensive Treatment, Conversion Therapy, Local Treatment

1. 引言

PVTT 是 HCC 分期、治疗选择和预后判断的重要影响因素。BCLC 分期将血管侵犯归入进展期，推荐系统治疗为主；但中国、日本和韩国等亚洲体系更强调 PVTT 解剖范围、肝功能储备和肿瘤可切除性，主张通过 MDT 选择手术、局部治疗和系统治疗的综合方案[1]-[3]。临床常用 PVTT 分型包括日本 Vp 分型和中国程氏分型。程氏分型将 PVTT 分为 I0、I、II、III、IV 型：I0 型为显微镜癌栓，I 型累及段或扇区门静脉分支，II 型累及左或右门静脉，III 型累及门静脉主干，IV 型累及肠系膜上静脉[4]。该分型较“有无血管侵犯”更能指导治疗选择和预后评估。2026 年中国肝癌合并门静脉癌栓诊治指南强化了系统治疗的重要性，为肝细胞癌合并 PVTT 的规范化诊疗提供最新循证依据[2]。

2. 局部治疗

2.1. TACE 治疗

TACE 通过栓塞肿瘤供血动脉导致肿瘤缺血。过往认为，伴 PVTT 的 HCC 是 TACE 的禁忌症，门静脉血供受损，进一步的肝动脉血供中断，可能导致肝脏坏死并引发肝衰竭[5]。但大量研究证实，只要肝功能良好且阻塞部位周围侧支循环充足，部分 PVTT 患者可以耐受 TACE [6]。一项回顾性研究发现，接受 TACE 治疗的节段性 PV 侵犯患者的 1 年、3 年和 5 年生存率分别为 44.9%、16.0%和 12.0% [7]。高肿瘤负荷、肝外转移、肿瘤对 TACE 反应不佳以及高 Child-Pugh 评分是预后不良的危险因素，不建议有 2~4 个危险因素的患者进行 TACE。Le [8]等也建议，对于仅有 0~1 个危险因素的患者，进行 TACE 可获得最大的生存获益和最小的不良反应。Luo [9]等通过前瞻性研究发现，节段性和主要 PVTT 均可从 TACE 中获益。在该研究中，9 例接受 TACE 的患者降期后接受了部分肝切除术(n = 6)或局部消融治疗(n = 3)，这些被认为是治愈性治疗，其中位 OS 长于其余仅接受 TACE 的 75 例患者(23.0 个月 vs. 6.3 个月，P < 0.01)。然而，Xiang [10]等持不同观点，他们发现 TACE 组 I、II、III、IV型 PVTT 患者的中位 OS 分别为 19、

12、9 和 6 个月，而最佳支持治疗组分别为 12、7、7 和 5 个月。因此，不建议IV型 PVTT 患者接受 TACE 治疗。

2.2. HAIC 治疗

HAIC 通过肝动脉持续灌注 FOLFOX、顺铂/5-FU 等方案，使肝内肿瘤和癌栓区域获得较高药物浓度。在 HCC-PVTT 中，HAIC 尤其适合肝内病灶主导、高肿瘤负荷、无广泛肝外转移且肝功能尚可的患者[11]。He 等的随机研究显示，索拉非尼联合 FOLFOX-HAIC 较索拉非尼单药显著改善 HCC 伴门静脉侵犯患者的总生存、无进展生存和客观缓解率[12]。FOHAIC-1 研究进一步显示，FOLFOX-HAIC 在进展期 HCC 中较索拉非尼具有更优疗效，支持 HAIC 作为进展期 HCC 的重要方案[13]。既往与索拉非尼、TACE/TAE 或其他方案比较的研究也提示，HAIC 在 PVTT 人群中具有较高肿瘤控制率[14]-[16]。近年来，HAIC 联合 TKI 或 PD-1/PD-L1 抑制剂成为研究热点。多项真实世界和倾向评分匹配研究显示，HAIC 联合仑伐替尼和 PD-1 抑制剂可改善 Vp4 PVTT 或主要门静脉癌栓患者的缓解率和生存结局[17]-[19]。虽然 HAIC 联合 TKI 或 PD-1/PD-L1 抑制剂在 Vp4 型 PVTT 中表现出较好的肿瘤控制能力，但仍需随机对照试验进一步证实。

2.3. 放射治疗

放疗可直接控制门静脉癌栓、促进门静脉血流恢复、降低肝内播散风险，包括三维适形放疗、调强放疗、立体定向放疗和质子治疗[20]-[22]。对于 Child-Pugh A 或部分 Child-Pugh B、肿瘤主要局限肝内、无严重腹水或黄疸的患者，放疗是重要局部治疗选择[2] [23]。Su 等人比较了 3D-CRT 与手术治疗，发现而 3D-CRT 对于 II 型和 III 型 PVTT 是一种有效的治疗措施[24]。立体定向放射治疗(SBRT)方面，Lee SJ 等人发现，对于门静脉主干或第一分支有肿瘤血栓的 HCC 患者，MRI 引导的肿瘤追踪 HFRT 和 SBRT 是一种可行、有效和安全的治疗选择，10 例患者(83.3%)显示 PVTT 客观缓解[25]。近年来，放疗联合免疫治疗及抗血管生成治疗取得重要进展。SBRT 联合卡瑞利珠单抗和阿帕替尼在 HCC-PVTT 中显示出较高反应率和可接受安全性[26]。Zhu 等的多中心单臂 II 期研究显示，信迪利单抗 + 贝伐珠单抗联合放疗作为一线治疗 HCC-PVTT 具有较好疗效和安全性，为“放疗 + 免疫 + 抗 VEGF”提供了前瞻性证据[27]。相关真实世界研究也提示，PVTT 放疗可能增强阿替利珠单抗 + 贝伐珠单抗或信迪利单抗 + 贝伐珠单抗的治疗效果[28] [29]。

3. 以转化切除为目标的联合治疗策略

随着系统治疗进入免疫联合时代，HCC-PVTT 的治疗模式已由单一局部治疗或单一系统治疗，逐渐转向多种治疗策略联合治疗。Zou [30]等回顾性分析 160 例 HCC 伴 PVTT 患者，其中采用联合仑伐替尼加 PD-1 抑制剂组的患者 OS、ORR、DCR 及无进展生存期均优于 TACE 联合仑伐替尼组(OS：23.5 个月 vs 18.3 个月，P = 0.0002；PFS：7.5 个月 vs 4.3 个月，ORR：80.00% vs 56.67%；DCR：38.57% vs 24.45%)，差异有统计学意义。TACE 处理肝内主体肿瘤，放疗精准聚焦于对 TACE 不敏感的 PVTT，两者联用具有很好的协同效果[31]。同时，放疗可引起肿瘤细胞免疫原性死亡，释放肿瘤抗原，改善肿瘤微环境的免疫抑制状态，从而可能增强后续免疫检查点抑制剂等免疫治疗的疗效。TACE 术后可引发肿瘤组织的缺血与缺氧状态，从而抑制肿瘤增殖并诱导其坏死。然而，该过程同时也会影响正常肝组织，造成其血供不足，进一步激活缺氧诱导因子和血管内皮生长因子等信号分子，促使侧支血管形成，而小分子类抗血管生成药物能够通过阻断血管内皮细胞生长因子受体的活性，有效遏制肿瘤进展。因此，在临床实践中 TACE 常与靶向药物联合应用[32]。

IMbrave150 研究确立了阿替利珠单抗 + 贝伐珠单抗在不可切除 HCC 一线治疗中的重要地位[33][34]。IMbrave150 Vp4 探索性分析显示，即使在门静脉主干和/或对侧门静脉侵犯患者中，阿替利珠单抗 + 贝伐珠单抗仍较索拉非尼显示疗效优势，但该人群总体预后仍较差[35]。因此，对于 Vp4 或主干型 PVTT 患者，免疫联合抗血管生成治疗是重要基础方案，但通常仍需结合局部治疗进一步提高肝内控制率。

信迪利单抗 + 贝伐珠单抗类似物、卡瑞利珠单抗 + 阿帕替尼、度伐利尤单抗 + 替西木单抗等方案也在进展期 HCC 中显示出疗效。但需要注意，部分大型 III 期研究并未纳入或充分覆盖门静脉主干癌栓患者，因此其结果外推到重度 PVTT 人群时需谨慎[36]。使用贝伐珠单抗或类似抗 VEGF 药物前，应常规评估食管胃底静脉曲张及消化道出血风险。

三联治疗常见组合包括 HAIC + 抗 VEGF + PD-1 抑制剂、TACE + 抗 VEGF + PD-1 抑制剂、放疗 + PD-1 抑制剂 + 抗 VEGF 治疗等。Zheng L 等人发现，TACE + 抗 VEGF + ICIs 组的疾病控制率高于 TACE + 抗 VEGF 组(81.82 vs. 55.17%, P = 0.046) [37]。一项荟萃分析显示，局部治疗联合靶向和免疫的三联方案较靶免双联可能改善 HCC-PVTT 患者 OS、PFS 和肿瘤反应率[38]。但也有研究指出，联合治疗不能做简单的加法，Hou X 等人指出，原始队列中 TACE-HAIC-TKI-PD-1 较 HAIC-TKI-PD-1 延长 PFS，但 OS 无差异，经倾向评分匹配后，两组 OS 和 PFS 均无统计学差异[39]。Krishnamurthy 等回顾性研究纳入 HCC 合并 PVTT、接受放疗联合免疫治疗的患者，结果显示中位 PFS 为 3.70 个月，中位 OS 为 7.70 个月。该结果提示，在 PVTT 人群中，放疗联合免疫治疗的真实世界疗效仍存在较大异质性，并非所有患者均能获得显著生存延长[40]。目前，三联治疗仍有待大型III期临床研究对疗效进一步验证，亚组分析有助于明确获益人群。

并非所有 HCC-PVTT 患者均适合转化治疗。目前多数指南推荐 PVTT I~IV 型、肝功能为 Child-Pugh A/B 级的患者，可依据实际情况使用放疗/TACE/HAIC + 靶向免疫等手段进行转化治疗以提高患者预后。HAIC 是 HCC-PVTT 转化治疗中的重要方案。FOLFOX-HAIC 可快速降低肝内肿瘤负荷和癌栓负荷，在部分患者中实现降期切除[13]。HAIC 联合仑伐替尼和 PD-1 抑制剂在 Vp4 PVTT 或主要门静脉癌栓患者中显示出较高缓解率，为转化切除提供了新的可能。TACE + RT 也是重要转化方案。TACE 控制肝内主灶，放疗控制门静脉癌栓，两者联合可在部分患者中实现癌栓退缩和病灶缩小[41]。Wang L 等人研究显示，对于最初不可切除的 HCC 和 PVTT 患者，通过三联治疗成功转换，93 例患者中，44 例接受了挽救手术，49 例未接受挽救手术。挽救手术组和非手术组的 OS 和 PFS 无显著差异[42]。因此，他们认为，对于转化成功的患者，可能不需要挽救性肝脏切除术，特别是对于 CR 或 III-IV 型 PVTT 患者。

目前转化治疗仍缺乏统一标准，包括最佳治疗周期、何时手术、是否要求影像完全缓解、是否需病理缓解、术后是否继续免疫或靶向治疗等[43]-[45]。应避免仅以影像缩小作为唯一依据，而应综合评估肿瘤生物学行为、AFP/PIVKA-II 动态变化、肝功能储备和可切除性。

4. 展望

HCC-PVTT 的治疗模式已由既往的单药治疗，逐步转向以系统治疗为基础、局部治疗与转化治疗协同推进的综合治疗时代。未来研究应进一步聚焦于 Vp4 或程氏 III-IV 型 PVTT 等高危人群的前瞻性随机对照研究，明确联合治疗的最佳组合方式。同时，鉴于 HCC-PVTT 患者常合并门静脉高压和食管胃底静脉曲张，贝伐珠单抗等抗 VEGF 药物应用前的出血风险评估与分层管理亟待规范化。对于真实世界中常见的 Child-Pugh B 级患者，未来需开展更多前瞻性研究，进一步明确不同肝功能储备状态下系统治疗、局部治疗的安全边界和获益人群，并制定更加个体化的治疗策略。未来应加强循环肿瘤 DNA (ctDNA)等新兴生物标志物及影像组学在疗效预测和患者筛选中的研究。同时，应更加重视患者报告结局(PROs)和生活质量评价，以更全面地评估治疗价值，改善患者长期预后[46]。总体而言，PVTT 作为进展期 HCC 的

不良分层因素，精细化的分层分析和联合治疗的进一步完善将为 HCC-PVTT 患者带来新希望。

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