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· 专题论坛 ·

侵犯肝中静脉的肝内胆管癌转化治疗的难点与策略

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摘要

肝内胆管癌 (ICC) 是一种起病隐匿、致死率极高的恶性肿瘤, 常因血管侵犯和转移, 导致无法进行根治性手术。肝中静脉 (MHV) 毗邻左右肝静脉和第二肝门, 是肝脏血管系统的重要组成部分, ICC 侵犯 MHV 的患者在治疗上面临较大的挑战, 且相关治疗决策常存在较多争议。转化治疗为最初不可切除的 ICC 患者带来了新的治疗希望, 尤其对于 ICC 侵犯 MHV 的患者而言, 转化治疗的需求尤为迫切。本文将结合相关研究成果和笔者团队的临床经验, 探讨 ICC 伴 MHV 侵犯在转化治疗中存在的若干难点问题, 旨在为此类患者的临床治疗提供参考。

关键词

胆管肿瘤; 胆管, 肝内; 肿瘤浸润; 肝中静脉; 转化治疗
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The challenges and strategies of conversion therapy for intrahepatic cholangiocarcinoma with middle hepatic vein invasion

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Abstract

Intrahepatic cholangiocarcinoma (ICC) is a malignancy with an insidious onset and extremely high mortality, often resulting in the inability to perform radical surgery due to vascular invasion and metastasis. The middle hepatic vein (MHV), located adjacent to the left and right hepatic veins and the second hepatic hilum, is an essential component of the hepatic vascular system. Patients with ICC involving the MHV face significant treatment challenges, and there is considerable debate regarding the optimal treatment decisions. Conversion therapy has provided new hope for patients with initially unresectable ICC, particularly for those with MHV invasion, who have an urgent need for such treatment. This article combines relevant research findings and clinical experience of the authors' team to discuss several challenges in conversion therapy for ICC with MHV invasion, aiming to provide reference for the clinical management of these patients.

Key words

Bile Duct Neoplasms; Bile Ducts, Intrahepatic; Neoplasm Invasiveness; Middle Hepatic Vein; Conversion Therapy
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肝内胆管癌 (intrahepatic cholangiocarcinoma, ICC) 是胆管细胞癌的一种亚型, 约占所有胆管癌 (cholangiocarcinoma, CCA) 的 10%~20%, 同时也是第二大常见原发性肝脏恶性肿瘤, 约占所有原发性肝癌的 10%^[1]。近年来, ICC 的发病率和病死率在全球范围内显著升高^[2-3], ICC 的 3、5 年的总生存率分别为 30% 和 18%^[4]。

肝中静脉 (middle hepatic vein, MHV) 是 ICC 常见受累血管, 约 15% 的 ICC 手术患者中存在 MHV 侵犯^[5]。半肝切除的 ICC 患者中, 近 40% 合并 MHV 侵犯^[5]。MHV 侵犯是肿瘤手术的相对禁忌证^[6], 血管扩大切除增加了患者的不良预后风险^[7]。此外, 解剖上, MHV 根部与左右肝静脉相邻, 增加了切缘阳性 (R₁ 切除) 的风险^[8-10]。不同患者 MHV 分支分布存在差异, 相应的不同肝段的引流也存在差异^[11-13], 因此治疗方式也存在差异^[5]。然而目前大多数研究多局限于血管侵犯或肝静脉侵犯层面, MHV 侵犯的类型尚未得到系统归纳, 且缺乏统一的标准。与此同时, MHV 侵犯的治疗方

案也未形成一致的规范^[14]。

转化治疗是指通过局部和/或全身的系统性治疗, 使最初不可切除或仅能进行姑息性切除的肿瘤转化为可根治性切除。目前转化治疗已在胆管癌治疗领域得到广泛应用, 显著提升中晚期患者的预后^[15-17]。鉴于 MHV 侵犯的普遍性和潜在危险性, 转化治疗的需求显得尤为迫切。本文将探讨合并肝中静脉侵犯的 ICC 患者在转化治疗过程中面临的相关挑战和难点。

1 MHV 侵犯的类型和切除性评估

1.1 侵犯 MHV 的 ICC 分型

根据肿瘤侵犯 MHV 静脉的解剖范围, ICC 侵犯 MHV 可分为以下四种类型: (1) I 型, 肿瘤只侵犯肝中静脉; (2) II 型, 肿瘤侵犯 2 支或 3 支肝静脉, 如肝中静脉和肝左静脉和 (或) 肝右静脉受侵犯; (3) III 型, 肿瘤侵犯肝中静脉和肝后下腔静脉; (4) IV 型, 肝中静脉侵犯同时合并双侧门静脉的侵犯 (图 1)。

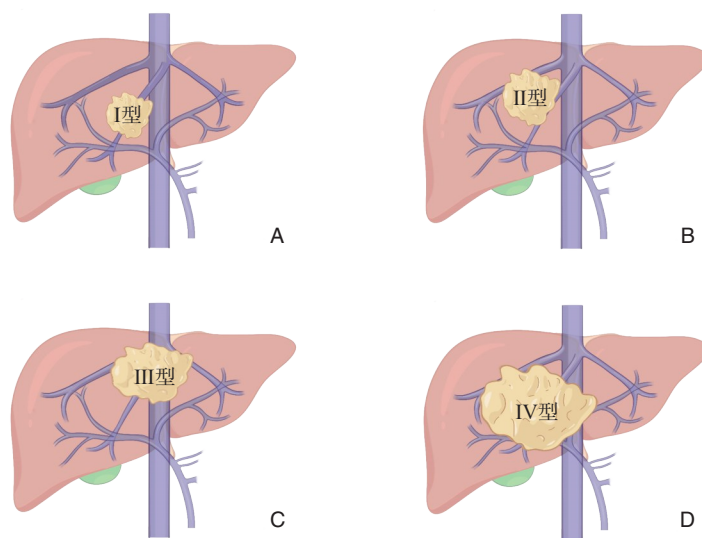


图 1 侵犯 MHV 的 ICC 四种类型 A: I 型, 肿瘤只侵犯 MHV; B: II 型, 肿瘤侵犯 2 支或 3 支肝静脉; C: III 型, 肿瘤侵犯 MHV 和肝后下腔静脉; D: IV 型, 肿瘤侵犯 MHV 和双侧门静脉

Figure 1 Four types of ICC with MHV invasion A: Type I, the tumor invades only the MHV; B: Type II, the tumor invades two or three branches of the hepatic veins; C: Type III, the tumor invades the MHV and the posterior inferior vena cava; D: Type IV, the tumor invades the MHV and bilateral portal veins

1.2 基于 MHV 分型的 ICC 的切除性评估

目前 ICC 可切除性尚无统一标准^[18-19], 美国肝胆胰协会将 ICC 可切除性定义为将完全切除肿瘤为目标, 肿瘤切除边缘为阴性 (R₀), 且留下足够的

剩余肝体积 (future liver remnant, FLR), 以维持正常生理活动所需的肝功能^[20]。与肝细胞肝癌不同, 判断可切除性时, 还需考虑有无肿瘤学不良预后因素, 欧洲肝脏研究联合会指南^[6]明确提出, ICC

合并淋巴结转移、血管侵犯、多结节的任一因素是可切除性的相对禁忌。基于指南和MHV分型,可在诊断时评估可切除性:I型可直接局部切除或肝中叶切除^[19]。如伴有淋巴结转移,提示存在生物学高危因素^[10,21]。在此情况下,除直接切除肿瘤并进行淋巴结清扫外,进行转化治疗也是另外一种选择^[22]。II~IV型如直接切除往往需行扩大肝切除,手术风险极大,需慎重决策。建议II~IV型优先考虑转化治疗,2~4个周期后评估治疗反应和转化切除的可行性(图2)。

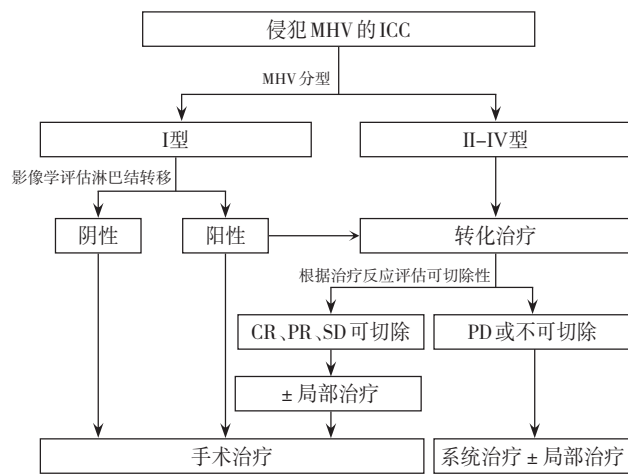


图2 基于MHV侵犯分型的ICC治疗流程图(CR:完全缓解;PR:部分缓解;PD:疾病进展;SD:疾病稳定)

Figure 2 Treatment flowchart of ICC based on MHV invasion classification (CR: complete response; PR: partial response; PD: progressive disease; SD: stable disease)

2 转化治疗方案的选择

目前有文献报告^[23-24]指出,化疗或化疗联合免疫检查点抑制剂作为MHV侵犯ICC的转化治疗方案,可使肿瘤缩小并改善肿瘤继续侵犯MHV。此外转化治疗后获得根治性切除的患者,与无法接受手术的患者相比生存期明显延长^[25]。然而目前转化治疗缺乏相关临床试验和随机对照试验数据,尚未形成统一的治疗标准。在临床实践中,通常以晚期胆道癌的标准一线治疗方案—吉西他滨联合顺铂为基础^[26-27],并根据患者具体情况联合其他药物,如化疗药物氟尿嘧啶、白蛋白结合型紫杉醇等^[28-29],免疫检查点抑制剂度伐利尤单抗、帕博利珠单抗等^[30-31],以及酪氨酸激酶抑制剂仑伐替尼

等作为探索性治疗^[32]。局部治疗通常作为全身系统治疗的后续方案,包括经导管动脉栓塞化疗、肝动脉化疗灌注治疗和立体定向放疗等,这些方法均已报道能对包括MHV侵犯在内的不可切除的ICC产生有效的降期效果^[33-37]。而射频消融、微波消融等局部消融治疗对侵犯MHV等大血管的ICC转化效果有限,通常不作为转化治疗方案的选择^[38-39]。

3 转化治疗后效果评估和手术安全性评估

3.1 转化治疗效果评估

根据实体瘤疗效评价标准RECIST1.1,基于CT、MRI、PET/CT影像学测定的肿瘤和淋巴结大小,转化治疗效果通常分为CR、PR、PD和SD^[40]。对于全身转化治疗后的SD患者,可联合局部治疗作为补救方案以尝试肿瘤降期,目前已有相关案例报道^[41]。对于全身联合局部转化治疗后仍维持SD的患者,经严格评估后,部分病例可通过扩大手术范围争取根治性切除的机会。对于PR患者,转化治疗效果显著,肿瘤已降期,符合手术条件,可进行手术^[42]。鉴于全身治疗联合局部治疗已有成功病例报道甚至实现了完全缓解的疗效,对于存在MHV侵犯的PR患者,在密切监测不良反应的前提下,可以考虑增加局部治疗^[41,43-44]。对于PD患者,由于首次转化方案失败,应根据进展期不可切除的系统治疗方案进行治疗,尽早调整药物方案,必要时可联合局部治疗以延缓疾病进展并延长生存时间^[43]。

3.2 转化治疗后手术安全性方案

对转化治疗CR、PR或SD的侵犯MHV的ICC患者而言,无严重的全身性疾病,并具备合格的身体功能状态是接受手术的前提条件^[45]。此外肝功能正常的患者至少需要20%的FLR^[46],考虑到药物和放射性治疗可能引起的肝毒性,转化治疗中存在肝功能损伤风险^[36,47],对于PR或SD的患者则至少需要30%的FLR,如伴肝硬化则至少需要40%的FLR^[46]。在FLR不足的情况下常面临血管切缘阳性R₁切除和切缘阴性R₀切除的选择,尽管R₁切除手术风险较小,但其是长期预后的显著不利因素^[9],扩大切除有助于降低切缘处肿瘤暴露的风险,从而提高生存率^[8]。

4 MHV侵犯手术方案的评估

4.1 MHV切除或重建方案的评估

血管重建手术在保证静脉切缘阴性的同时,可使剩余肝段具备完整的流出道,降低术后肝衰竭的风险。然而重建手术存在血管口径不匹配、额外手术创伤及较长的手术时间等问题^[48-49]。不同MHV分型对于血管重建的需求不同。II型如包绕全部3支肝静脉,则需进行全肝静脉系统重建^[48],III型如侵犯3支肝静脉的共同汇合区,需行肝静脉主干重建以保障流出道通畅^[50],IV型累及双侧门静脉,需考虑联合门静脉重建^[51]。然而,对于侵犯2支肝静脉(肝左静脉或肝右静脉)的II型ICC是否需进行MHV重建存在争议,有研究^[8]表明,部分该类型患者可以考虑单纯切除MHV。

4.2 MHV单纯切除的理论依据

MHV独特的解剖学结构和生理学特性是可单纯切除而非重建的关键。据报道MHV的分支可分为三型:I型(59%),由IVB段和V段分支静脉形成主干,接受IVA段及VIII段的静脉汇入;II型(23%),为单独主干,全程接收邻近组织的回流静脉血;III型(18%),整体与I型相似,但右侧分支延伸到VI段^[12-13]。同时肝段的静脉引流也存在差异,如约37.7%的IVB段主要由MHV引流,而约62.3%的IVB段静脉由左肝静脉引流^[11]。生理学上动物实验证实了肝脏具备自发性血运重建的机制,在大鼠右肝静脉阻断后,2d内可观察到流出道梗阻区的肝功能显著下降。然而随着血运重建,7d后局灶性流出道梗阻可恢复至术前水平^[52]。因此尽管单纯MHV切除可能导致剩余IV、V、VIII段等在短期内出现流出道梗阻和肝功能下降,但血运重建后,流出道梗阻和肝功能下降存在逆转可能。此外研究也报道MHV切除与重建之间的术后肝衰竭发病率无显著差异^[5],FLR足够的患者,MHV切除不会造成肝功能衰竭^[8,53]。

4.3 MHV单纯切除的注意事项

虽然远期效果来看,MHV切除不影响肝功能和预后,然而短期内可能增加肝衰竭风险,值得重视。考虑到肝功能损伤的严重程度及其自发恢复时间与其引流通道相关^[52],针对转化治疗后FLR可能不足的MHV侵犯的ICC患者,MHV分支引流情况是决定重建或单纯切除手术方案的关键因素。目前基于CT、MRI、PET/CT等影像的计算机辅助

技术能够对血管结构进行三维重建,计算肝体积,并对MHV的优势关系进行风险分析^[54-55]。因此在侵犯MHV的ICC转化治疗手术前,应基于计算机辅助三维重建技术,充分评估MHV的引流情况,决定合适的手术方案,尽可能减少不必要的手术操作,同时有效保障术后肝功能,避免肝衰竭等并发症。

5 总结和展望

基于肿瘤侵犯静脉的范围,可将侵犯MHV的ICC分为四型,并结合淋巴结状态,对ICC的可切除性进行评估。转化治疗为不可切除的患者提供了根治性手术的机会^[16,19]。目前转化治疗方案尚无统一共识,但晚期胆管癌的一线治疗方案仍是临床优先采用的策略。对于转化治疗后CR、PR和SD且具备可切除条件的患者,术前可考虑结合局部治疗提高根治性切除可能。术前应判断R₀切除后FLR是否足够,评估MHV等受累血管的解剖位置和引流功能,以帮助确定是否保留、切除或重建相关静脉。近年来,人工智能、基因检测、液体活检和类器官等技术的多样化发展^[56-58],提升了侵犯MHV的ICC患者的转化治疗的成功率,给患者预后带来了新的希望。

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