·专家论坛·

DOI：10.12449/JCH251203

肝内胆管癌局部治疗及系统治疗研究进展

刘　洋[1]，施祥德[2]，刘明奇[2]，刘　超[2]

1 贵州医科大学附属医院肝胆外科，贵阳 550000

2 中山大学孙逸仙纪念医院胆胰外科，广州 510000

通信作者：刘超，liuchao3@mail.sysu.edu.cn（ORCID：0000-0001-6659-4372）

摘要：肝内胆管癌（iCCA）是一种侵袭性强、预后极差的恶性肿瘤，近年来发病率逐年上升。本文简述了iCCA的主要局部治疗方式，并回顾了系统治疗的进展，重点评述了局部治疗联合靶向及免疫治疗的研究现状，分析其在提高客观缓解率、延长无进展生存期和总生存期方面的优势。文章指出，免疫联合化疗已成为不可切除iCCA的一线治疗标准，而局部治疗联合靶向免疫模式在早期研究中显示出更高的转化潜力和持久疗效。作者认为，未来应通过多中心、前瞻性研究进一步验证疗效与安全性，明确最佳联合模式与适应人群，为iCCA综合治疗提供新思路。

关键词：肝内胆管癌；局部治疗；系统治疗

基金项目：广州市科技计划项目（2024A04J4776）；中山大学中央高校基本科研业务费专项资金临床研究5010计划资助（2018008）；广州市临床重大技术建设项目（2023P-ZD17）

Research advances in local treatment and systemic therapy for intrahepatic cholangiocarcinoma

LIU Yang[1], *SHI Xiangde*[2], *LIU Mingqi*[2], *LIU Chao*[2]

1. Department of Hepatobiliary Surgery, The Affiliated Hospital of Guizhou Medical University, Guiyang 550000, China;

2. Department of Biliary-Pancreatic Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou 510000, China

Corresponding author: LIU Chao, liuchao3@mail.sysu.edu.cn (ORCID: 0000-0001-6659-4372)

Abstract: Intrahepatic cholangiocarcinoma (iCCA) is a highly aggressive malignant tumor with poor prognosis, and its incidence rate is gradually increasing in recent years. This article reviews the main local treatment methods for iCCA and the advances in related systemic therapies, with a focus on the current status of research on local treatment combined with targeted therapy and immunotherapy, highlighting their advantages in improving objective response rate and prolonging progression-free survival and overall survival. This article points out that immunotherapy combined with chemotherapy has become the first-line standard treatment for unresectable iCCA, while the regimen of local treatment combined with targeted therapy and immunotherapy has shown promising potential in clinical translation and sustained efficacy in early-phase studies. The authors believe that in the future, multicenter prospective studies are needed to verify the efficacy and safety of the above treatment regimen, determine the optimal combined treatment regimen, and define suitable patient populations, in order to provide new ideas for the comprehensive treatment of iCCA.

Key words: Intrahepatic Cholangiocarcinoma; Local Treatment; Systemic Therapy

Research funding: Science and Technology Projects in Guangzhou (2024A04J4776); Fundamental Research Funds for the Central Universities, Clinical Research 5010 Program, Sun Yat-sen University (2018008); Major Clinical Technology Program of Guangzhou Municipal Health Commission (2023P-ZD17)

肝内胆管癌（intrahepatic cholangiocarcinoma，iCCA）起源于肝内胆管上皮细胞，侵袭力强且预后极差，5年存活率低于5%。在肝脏原发性恶性肿瘤中，iCCA发病率仅次于肝细胞癌（HCC），占原发性肝癌的10%～15%，占

所有消化道肿瘤的3%[1-2]。iCCA发病率在世界范围内呈明显上升趋势[3],亚洲人群胆管癌发病率明显高于欧美人群[4]。吸烟、超重、肝硬化、胆囊结石和胆管结石均为胆管癌发生的高危因素。此外,城市人群较多食用鱼生,山区寄生虫感染高发也是胆道恶性肿瘤的诱因[4]。

目前,手术切除仍是iCCA唯一的根治性治疗手段,但只有20%~30%的iCCA患者可行根治性手术切除[5],即使可切除患者的5年生存率也只有20%~35%[6],且大多数仍会复发,iCCA根治性切除术后的切缘复发率为24%,肝内复发率为29%,肝外复发率高达47%[7]。由于iCCA早期缺乏特异性临床症状,大多数患者确诊时已处于中晚期[5,8]。对于无法行根治性切除的iCCA患者,介入治疗以及系统治疗占重要地位。

虽然近年来多学科综合治疗(包括系统化疗、靶向治疗和免疫治疗)取得了一定进展,但局部治疗仍是不可切除iCCA(uiCCA)患者的重要治疗选择[7]。局部治疗包括消融、经导管动脉化疗栓塞(transarterial chemoembolization, TACE)、放射性栓塞(transarterial radioembolization, TARE)及经导管肝动脉灌注化疗(hepatic artery infusion chemotherapy, HAIC)等。对于不可手术切除且不适于消融治疗、局限于肝脏的iCCA,TACE、TARE和肝动脉灌注等介入疗法是重要的局部治疗选择。近年来,随着靶向治疗和免疫治疗的发展,动脉介入治疗与全身治疗的联合应用展现了巨大的潜力。如TACE联合靶向药物仑伐替尼(Lenvatinib)或免疫检查点抑制剂(immune checkpoint inhibitor, ICI)在改善患者预后方面疗效显著[9-10]。

本文旨在探讨局部治疗与全身治疗联合应用干预iCCA的协同效应,并对该领域的现有证据及正在进行的研究进行综述。

1 局部治疗

1.1 TACE TACE按给药方式分为传统cTACE与载药微球D-TACE。cTACE将化疗药物与碘化油乳剂经导管注入肝动脉肿瘤供血分支,再以微球、吸收性明胶海绵或聚乙烯醇颗粒栓塞,既阻断血供又延缓药物洗脱。常用药物包括顺铂、多柔比星、丝裂霉素、伊立替康或组合。既往报道其治疗uiCCA客观缓解率(objective response rate, ORR)为10%~50%,中位总生存期(median overall survival, mOS)为12~20个月[11-15]。主要不良事件为肝酶升高及栓塞后综合征;最常见死亡原因为急性肝功能不全,其次为感染与消化道出血。

D-TACE以载药微球为载体,常见有DC/LC Bead与HepaSphere。前者经离子交换在球体表面搭载阳离子药物并缓释,后者可在微球表面及内部装载药物,进入血管后发生膨胀,从而加强栓塞效果。在HCC中,D-TACE较cTACE应答率更高、毒性相近或更低[16-17]。一项前瞻性研究比较cTACE(丝裂霉素C)、iDEB-TACE(伊立替康)与全身化疗[吉西他滨+奥沙利铂(GEMOX)]在uiCCA中的疗效,iDEB-TACE的无进展生存期/总生存期(PFS/OS)为3.9/11.7个月,优于cTACE的1.8/5.7个月,与全身化疗(GEMOX)的6.2/11.0个月相当[18]。另一项纳入40例uiCCA的前瞻性研究显示,DEB-TACE治疗的1、3个月ORR(70% vs 20%;50% vs 15%)及中位无进展生存期(mPFS)(8.0 vs 3.0个月)均优于cTACE,OS无显著差异(12.5 vs 9.0个月),主要并发症为栓塞后综合征[19]。与cTACE相比,D-TACE在iCCA中表现为更高的应答率与更长的PFS,二者安全性相近,但对OS的提升尚不一致;治疗选择应结合肝功能储备、肿瘤负荷与个体耐受性综合评估。

1.2 TARE TARE通过经肿瘤供血动脉注射钇-90(^{90}Y)标记的放射性微球,使其富集于肿瘤内部,从而实现肿瘤局部辐射剂量的最大化,并尽量减少对周围正常肝组织的损伤。与DEB-TACE中使用的微球相比,^{90}Y微球不仅数量更少、栓塞负荷较低,而且因其体积更小,能够更深入地穿透肿瘤。在过去的十年中,^{90}Y已成为治疗uiCCA的一种日益流行的局部治疗方式。一项系统综述/荟萃分析(n=921)报道TARE术后mPFS为7.8个月(95%*CI*:4.2~11.3, I^2=94%)、OS为12.7个月(95%*CI*:10.6~14.8, I^2=62%),疾病控制率(disease control rate, DCR)为82.3%,转化切除率为11%[20]。该结果表明,TARE在uiCCA患者中显示出稳定且可重复的疾病控制效果及生存获益。

1.3 HAIC HAIC通过导管将化疗药物持续输注至肝动脉,为肿瘤提供高浓度药物,其优势包括无需栓塞剂、药物局部浓度高等。多数uiCCA局限于肝脏,HAIC能将高剂量化疗药物靶向输送至肝内肿瘤,肝脏有关代谢可降低系统毒性,尤其适用于肝内进展期病例。

一项荟萃分析收集了TACE(常规或药物洗脱珠,22项研究,1 145例患者)和肝动脉化疗(16项研究,331例患者)的相关数据,二者的ORR分别为6.3%和41.3%,mPFS分别为15.0个月和10.1个月,mOS分别为15.9个月和21.3个月[21]。另一项纳入20个研究657例患者的荟萃分析结果显示:与常规TACE、载药微球-TACE、钇90微球放疗栓塞比较,HAIC的肿瘤缓解率最高,患者总生存获益最大、Ⅲ~Ⅳ级不良反应发生率也较多[22]。3项Ⅱ期前瞻性试验对HAIC在uiCCA患者中的应用进行了探索,mOS为25.0~29.5个月,相对于全

身静脉化疗，HAIC可明显改善生存时间[23-25]。此外，一项回顾性研究分析2000—2018年共573例iCCA患者的研究结果显示：对于具有淋巴结转移的iCCA患者，接受根治性切除（mOS为19.7个月）或HAIC（mOS为18.1个月）的生存率没有差异，但接受根治性切除及HAIC的iCCA患者生存率优于单纯系统治疗（mOS为11.2个月）[26]。

1.4 *消融治疗* 经皮消融是一种成熟且广泛应用于原发性和继发性肝癌的局部治疗技术。在CT或超声引导下，将消融针置入肿瘤内，通过物理或化学方式杀死肿瘤细胞。主要方式包括射频消融（radiofrequency ablation，RFA）、微波消融和冷冻消融。目前消融治疗iCCA病例尚未见随机对照试验相关研究。RFA是治疗iCCA最早且使用最多的热消融方式。一项前瞻性研究评估了超声引导经皮RFA治疗iCCA的效果，10例病理确诊患者（肿瘤直径1.9～6.8 cm，12个疗程）术后经动态增强CT随访，总体完全坏死率为80%（≤3 cm组为100%，3.1～5 cm组为67%，>5 cm组为50%）。2例大肿瘤（4.7 cm、6.8 cm）出现残余强化灶，仅1例发生胆汁瘤，无严重并发症。该研究结果提示，RFA对≤3 cm的iCCA可能实现根治性消融，对3.1～5 cm疗效良好，但对>5 cm疗效有限[27]。

2 系统治疗

2.1 *化疗* 过去数十年，吉西他滨+顺铂（GC）或GEMOX等双联化疗方案被广泛用于晚期胆管癌的治疗，但其中位生存期仍不到1年。日本一项3期临床试验提出另一种方案Gem+S-1（Gem/S-1），该策略不劣于GC[中位生存期：GC为13.4个月，Gem/S-1为15.1个月；风险比（*HR*）=0.945，90%*CI*：0.78~1.15，*P*=0.046]。GC组mPFS为5.8个月，Gem/S-1组mPFS为6.8个月（*HR*=0.86，95%*CI*：0.70~1.07）[28]。

与标准二联化疗相比，三联化疗在晚期胆道癌中的治疗结果存在差异。Ⅲ期KHBO1401-MITSUBA研究共纳入246例患者，比较GC与吉西他滨+顺铂+S-1（GCS）方案。结果显示，GCS显著延长mOS（13.5个月 vs 12.6个月，*HR*=0.79，*P*=0.046），提高PFS（7.4个月 vs 5.5个月，*HR*=0.75，*P*=0.015）及ORR（41.5% vs 15.0%），且≥3级血液毒性无明显增加[29]。而在Ⅲ期SWOG S1815研究中，三联方案（GAP）虽在OS（14.0个月 vs 13.6个月）和PFS（7.5个月 vs 6.3个月）方面略有延长，但无统计学差异（OS：*HR*=0.91，*P*=0.41；PFS：*HR*=0.89，*P*=0.32），且≥3级血液毒性增加（60% vs 45%）。亚组分析提示，局部进展患者在GAP方案下的OS（19.2个月 vs 13.7个月）及PFS显著改善，提示潜在获益人群[30]。同样，在法国PRODIGE38AMEBICA试验中，改良FOLFIRINOX（mFOLFIRINOX）与标准GC方案相比，mPFS（6.2个月）和mOS（11.7个月）均略低于GC组（7.4和14.3个月），不良事件发生率相近（72%）[31]。三联化疗（如GCS、GAP）在部分研究中显示出一定的生存获益，但整体疗效提升有限且血液毒性增加。现有证据提示其可能适用于局部进展或体能良好的患者。

2.2 *靶向治疗*

2.2.1 *成纤维细胞生长因子受体2（fibroblast growth factor receptor 2，FGFR2）融合/重排* FGFR2融合仅见于10%～15% iCCA患者中，且多见于年轻患者[32]。一项纳入大量iCCA人群（*n*=6 130）的分子分析显示，576例患者（9.4%）存在FGFR2基因重排[33]；FGFR的突变可导致FGFR信号通路异常激活，从而促进细胞增殖、侵袭及血管生成等致癌过程[34]；根据FIGHT-202多中心单臂Ⅱ期试验（研究对象为既往接受过治疗的晚期胆管癌患者147例，其中iCCA 132例），107例携带FGFR2重排或融合并接受非选择性FGFR抑制剂培米替尼治疗的iCCA患者，中位随访时间为17.8（11.6～21.3）个月，ORR为35.5%，mPFS和mOS分别为6.9（95%*CI*：6.2～9.6）个月和21.1（95%*CI*：14.8～未达）个月[35]。近期该研究公布最终结果，在中位随访45.4个月后，中位缓解持续时间为9.1（6.0～14.5）个月，mPFS和mOS分别为7.0（6.1～10.5）和17.5（14.4～22.9）个月，大多数患者治疗中出现的不良事件为1～2级；最常见的≥3级的不良事件是低磷血症（14.3%）[36]。

2.2.2 *异柠檬酸脱氢酶（isocitrate dehydrogenase，IDH）突变* IDH1在西方iCCA人群中突变率为25%[37]。Lin等[38]对475例中国人群iCCA患者进行系统基因组分析，发现IDH1/2突变与FGFR2融合、乳腺癌1号关联蛋白突变等共现，常见于源自小胆管的iCCA分子亚型，伴有低水平糖类抗原19-9及较好预后，该研究提示中国人群胆管癌IDH突变率低于西方人群。IDH1属于IDH蛋白家族，其突变后的酶具有新功能，能够将α-酮戊二酸（α-KG）转化为2-羟基戊二酸（2-HG）。2-HG被认为是一种致癌代谢物，其积累可引发多种表观遗传改变[39]。Ivosidenib是一种针对IDH1突变的靶向药物，多项研究显示其对晚期iCCA有治疗作用。根据ClarIDHy研究（一项纳入185例对既往治疗无效的iCCA患者的多中心Ⅲ期随机对照试验），Ivosidenib与安慰剂相比，在PFS方面显示出显著改善的结局，*HR*为0.37（95%*CI*：0.25～0.54），mPFS分别为2.7个月和1.4个月。Ivosidenib耐受性良好，其安全性与安慰剂组相当[40]。该研究公布的最

终结果显示，OS虽在数值上有所提高，但尚未达统计学差异[mOS：10.3（95%*CI*：7.8～12.4）个月 vs 7.5（95%*CI*：4.8～11.1）个月，*HR*（95%*CI*）：0.79（0.56～1.12），*P*=0.09]。在调整交叉用药后，安慰剂组mOS为5.1（95%*CI*：3.8～7.6）个月，*HR*降为0.49（95%*CI*：0.34~0.70）（*P*<0.001）[40-41]。

2.2.3 人表皮生长因子受体（human epidermal growth factor receptor，HER2） 相比于肝外胆管癌，iCCA中HER2过表达比例较低[38,42]。一项研究对304例iCCA样本进行免疫组化和荧光原位杂交检测，最终发现4.27%（13/304）的样本存在HER2扩增，荧光原位杂交与免疫组化在iCCA中一致性较差。HER2扩增病例具有更高的肿瘤突变负荷，尽管免疫标志物整体无显著差异，但HER2扩增组中$CD8^+CTLA4^+$和$CD8^+FOXP3^+$细胞密度增加，提示其具有独特的免疫抑制微环境特征[43]。一项Ⅱ期临床研究（KCSG-HB19-14）显示，在GC方案治疗失败后，HER2阳性的晚期胆管癌患者接受Trastuzumab联合FOLFOX化疗，ORR为29.4%，mOS为10.7个月，未报告转化治疗成功的病例。MyPathway胆道肿瘤（BTC）Ⅱ期队列研究调查了帕妥珠单抗（pertuzumab）联合曲妥珠单抗（trastuzumab）在既往接受过治疗且携带HER2扩增的晚期BTC患者中的疗效，共纳入39例患者，总体ORR为23%，mPFS和mOS分别为4.0（95%*CI*：1.8～5.7）个月和10.9（95%*CI*：5.2～15.6）个月[44]。然而，这些研究仅纳入少量的iCCA病例。

2.2.4 多靶点激酶抑制剂 Lenvatinib是一种口服多靶点酪氨酸激酶抑制剂（tyrosine kinase inhibitor，TKI），可同时抑制血管内皮生长因子受体1～3、FGFR1～4、血小板衍生生长因子受体α、RET及KIT，已广泛应用于包括肝癌在内的多种恶性肿瘤的治疗[45-47]。然而，其单药用于晚期胆管癌的疗效有限。一项Ⅱ期单臂研究纳入了26例晚期胆管癌患者（其中iCCA 6例），结果显示ORR为11.5%，mPFS为1.64（95%*CI*：1.41～3.19）个月，mOS为7.35（95%*CI*：4.50～11.27）个月[48]。在联合治疗中，Lenvatinib表现出显著疗效提升。一项Ⅱ期临床研究评估其联合托瑞帕利单抗及GEMOX用于晚期iCCA一线治疗，结果显示ORR高达80.0%（95%*CI*：61.4%～92.3%），DCR为93.3%（95%*CI*：77.9%～99.2%），mPFS为10.2（95%*CI*：6.7～13.8）个月，mOS为22.5（95%*CI*：16.2～未达）个月。其中携带DNA损伤修复基因突变的患者反应更佳[49]。

2.3 免疫治疗 ICI单药治疗胆管癌的疗效总体有限。Ⅱ期KEYNOTE-158研究纳入104例经标准化疗后进展的晚期胆道癌患者，帕博利珠单抗（Pembrolizumab）治疗的ORR为5.8%，mPFS为2.0个月，mOS为7.4个月。KEYNOTE-028试验中24例患者的ORR为13%，mPFS为1.8个月，mOS为5.7个月。值得注意的是，两项研究中6%～13%的患者可获得长期缓解（持续6个月至4年以上），且与程序性细胞死亡配体1（programmed death-ligand 1，PD-L1）表达无明显相关[50]。另一项纳武利尤单抗（nivolumab）Ⅱ期研究显示，ORR为11%，DCR为50%，mPFS为3.68个月，mOS为14.24个月。部分获益患者伴有DNA错配修复缺陷或较高程序性细胞死亡受体1（programmed cell death protein 1，PD-1）表达[51]。总体而言，免疫单药治疗虽仅使少数患者受益，但在特定分子亚型中显示出持久疗效，提示免疫治疗在胆管癌中的潜在应用价值及患者筛选的重要性。

双免方案在HCC中表现出稳定持续的临床获益[52]，但在iCCA中的效果相对有限。CA209-538研究评估了Nivolumab联合Ipilimumab治疗晚期BTC的疗效，总体ORR为23%，mPFS为2.9个月，OS为5.7个月。部分患者（尤其PD-L1阳性）获得持续缓解，应答者主要集中在胆囊癌和iCCA，提示免疫反应可能与肿瘤部位相关[53]。另一项发表于*Cancer*的Ⅱ期随机研究比较了Nivolumab+Ipilimumab与Nivolumab+GC的疗效。结果显示，双免组ORR为22%，PFS为3.9个月，OS为8.2个月；而Nivolumab+GC组ORR为35%，PFS为6.6个月，OS为10.6个月，且后者在PFS方面具有显著优势（*HR*=0.51，*P*=0.03）。两组毒性安全可控，但双免组3级以上免疫相关不良事件较多（30% vs 22%）[54]。双免方案虽可在部分iCCA患者中诱导持久缓解，但总体疗效有限；相比之下，免疫联合化疗方案在缓解率及生存获益方面表现更优。

TOPAZ-1研究为Ⅲ期随机、双盲、安慰剂对照试验，共纳入658例晚期胆管癌患者（其中iCCA占56%），比较Durvalumab联合GC与安慰剂联合GC的疗效。结果显示，Durvalumab组mOS为12.8个月，mPFS为7.2个月，ORR为26.7%，高于安慰剂组的mOS［11.5个月（*HR*=0.80，*P*=0.021）］、mPFS［5.7个月（*HR*=0.75，*P*=0.001）］、ORR（18.7%）。两组不良事件发生率相近，安全性良好[55]。此外，在Ⅲ期KEYNOTE-966试验中，1 069例晚期BTC患者随机接受帕博利珠单抗（Pembrolizumab）联合GC或安慰剂联合GC治疗（其中iCCA占40%）。联合组mOS显著延长（12.7个月 vs 10.9个月，*HR*=0.83，*P*=0.003 4），ORR亦提高（29% vs 20%），在iCCA亚组中获益一致，毒性安全可控，确立了免疫联合化疗作为一线治疗的重要地位[56]。此外，一项Ⅱ期研究评估仑伐替尼联合托瑞帕利单抗及GEMOX治疗晚期iCCA的疗效，

30例患者中ORR达80.0%，DCR为93.3%，mPFS为10.2个月，OS为22.5个月，显示出显著的抗肿瘤活性和持久反应。该方案的Ⅲ期验证性研究（NCT03951597）正在进行中[49]。综上，TOPAZ-1与KEYNOTE-966研究确立了免疫联合化疗作为晚期iCCA标准一线治疗的基础，而仑伐替尼联合免疫及化疗方案在早期研究中表现出更高的缓解率与更长生存期，提示免疫联合靶向与化疗的多模态治疗将成为未来iCCA系统治疗的关键方向。

3 局部治疗联合靶向免疫治疗

3.1 *作用机制* 在iCCA中，局部联合靶免治疗的相关机制研究甚少，而在HCC中，有研究显示局部治疗联合全身治疗可增强抗肿瘤免疫[57]。局部治疗（如TACE、HAIC、RFA、放射治疗）不仅限于局部作用，其诱导的肿瘤细胞死亡可释放抗原和损伤相关分子模式，进而激活抗原提呈，启动全身免疫反应[58]。例如，在HCC中，TACE可诱导免疫原性细胞死亡，将免疫抑制型的肿瘤微环境转变为免疫激活型[59]。TACE可使肿瘤组织坏死，从而减少免疫抑制因子的释放，并减轻对免疫功能的抑制[60]。此外，坏死的肿瘤组织还可通过改变外周免疫细胞的表型，激活系统性免疫反应[61]。HAIC可将高浓度化疗药物（如吉西他滨、顺铂及奥沙利铂等）输送至肝脏，并且这些药物能促进肿瘤细胞释放抗原和刺激信号，促进树突状细胞成熟及$CD8^+$T细胞活化，从而增强抗原提呈与免疫原性[62]。仑伐替尼等TKI通过靶向血管内皮生长因子和FGFR通路，不仅能减少免疫抑制剂分泌，还可有效削弱免疫抑制性细胞如髓源性抑制细胞、调节性T细胞和M2型肿瘤相关巨噬细胞在肿瘤局部的浸润，进而缓解肿瘤微环境的免疫抑制状态[63-64]。此外，仑伐替尼对血管生成的抑制还可促进血管正常化，改善免疫细胞和药物进入肿瘤组织的能力，为ICI、化疗等药物的协同作用提供有利条件[65-66]。

3.2 *临床研究进展* 在多项多中心或单中心回顾性研究中，HAIC（多采用FOLFOX或GEMOX方案）联合靶向治疗与PD-1或PD-L1抑制剂在iCCA中均表现出较好的疗效。Lin等[67]在一项三队列对照研究中发现，接受HAIC+仑伐替尼+PD-(L)1治疗（HLP组）的一线患者，其ORR达50%，mPFS为30.0个月，显著优于接受系统化疗±免疫治疗的对照组（ORR仅为6%～18.4%，PFS为6.5～10.2个月）。Xu等[68]在另一项倾向评分匹配的研究中也观察到相似结果，HLP组的ORR为56.7%，mPFS达11.17（95%*CI*：7.0～26.7）个月，mOS达16.91（95%*CI*：11.6～28.4）个月。Zheng等[69]研究中纳入152例患者，比较HAIC+靶向+PD-1联合治疗与传统系统化疗，发现三联治疗组的ORR、mPFS和mOS分别为35.5%、9.07个月和20.77个月，均优于对照组。在非对照的单臂研究中，也呈现出类似趋势。Huang等[70]在一项纳入46例iCCA患者的回顾性研究中报道，FOLFOX-HAIC联合仑伐替尼与PD-1抑制剂治疗的ORR达47.8%，mPFS为9.4（95%*CI*：5.28～13.52）个月，mOS达16.77（95%*CI*：14.20～19.33）个月，且免疫活性高（如$CD8^+$T细胞浸润）与治疗反应呈正相关，而肿瘤突变负荷与预后无关。Zhao等[71]研究则显示，在一线应用FOLFOX-HAIC+仑伐替尼+Durvalumab治疗的28例患者中，ORR为39.1%，mPFS和mOS分别为11.9（95%*CI*：5.7～30.1）个月与17.9（95%*CI*：6.7～17.1）个月。部分研究还比较了HAIC与其他局部治疗模式的联合效果。Zhang等[72]在比较HAIC+TKI+PD-1与TACE+TKI+PD-1治疗iCCA的研究中发现，HAIC组合具有更高的ORR（48.7% vs 15.8%）与1年PFS率（61.9% vs 31.6%），提示在与TKI/免疫治疗联合时，HAIC可能优于TACE。在安全性方面，大多数研究报道该三联方案整体耐受性良好，≥3级不良事件发生率为40%~66%，主要包括中性粒细胞减少、血小板减少、转氨酶升高、乏力及恶心呕吐等，极少数患者出现免疫相关严重毒性反应。2025年美国临床肿瘤学会年会公布REACH-01研究初步结果，该研究采用HAIC联合TAE与替雷利珠单抗及索凡替尼（一种口服小分子多靶点TKI）治疗uiCCA。研究共纳入28例患者，在中位随访9.33个月后，ORR为57.69%，DCR为80.77%，转化手术切除率为15.38%，32.14%患者出现可控的3级以上不良事件，最常见的为丙氨酸氨基转移酶升高（7.14%）、厌食（7.14%）及低钾血症（7.14%），未出现因不良事件导致治疗中断或死亡[73]。尽管尚无前瞻性Ⅲ期随机研究验证“HAIC+TKI+ICI”优于TOPAZ-1或KEYNOTE-966等免疫化疗方案，但这些真实世界数据及前瞻性单臂研究为其潜在临床价值提供了初步证据。总结HAIC联合靶向免疫治疗iCCA相关报道见表1。

在TACE联合靶向免疫方面，Yang等[10]通过倾向评分匹配比较了uiCCA患者接受DEB-TACE+ICI与标准化疗（GC）的疗效。结果显示联合治疗组的ORR为55.0%（化疗组为20.0%，*P*=0.022），mPFS为7.2个月（化疗组为5.7个月，*P*=0.036），mOS为13.2个月（化疗组为7.6个月，*P*=0.015）；两组治疗相关不良事件发生率相似，耐受性良好。Liu等[81]开展的多中心倾向评分匹配回顾研究发现，与系统化疗+ICI对照组相比，DEA-TACE联合系统化疗及ICI观察组在肿瘤控制率及生存时间方面显著改善，观察组患者ORR为76.06%、DCR为97.18%，均显著高于对照组（52.11%、85.92%），PFS为

表1 HAIC联合靶向免疫治疗iCCA相关研究

Table 1 Research on HAIC combined with targeted therapy and immunotherapy for iCCA

作者(发表年)	研究设计	疾病	样本量	ORR(%)	DCR(%)	mPFS(月)	mOS(月)	≥G3 AE
Lin[67](2024)	回顾性三队列；HLP：HAIC+仑伐替尼+PD-(L)1；SCP：系统化疗+PD-(L)1；SC：化疗	iCCA	HLP：42 SCP：49 SC：50	50.0 vs 18.4 vs 6.0	88.1 vs 69.4 vs 46.0	30.0 vs 10.2 vs 6.5	NR vs NR vs 21.8	tHLP组≥G3~4 AE更少
Xu[68](2025)	回顾性双臂；HAIC(FOLFOX/GEMOX)+仑伐替尼+PD-1 vs 系统化疗	iCCA	86(PSM 30/30)	56.7 vs 23.3	93.3 vs 70.0	11.17 vs 5.55	16.91 vs 11.06	两组相当
Zheng[69](2025)	回顾性双臂；FOLFOX-HAIC+TKI+PD-1 vs 系统化疗	iCCA	76 vs 76(after PSM)	35.5 vs 14.5	76.3 vs 60.5	9.07 vs 6.23	20.77 vs 14.83	三联组ALT升高较多
Huang[70](2024)	回顾性单臂；FOLFOX-HAIC+仑伐替尼+PD-1	iCCA	46	47.8(mRECIST 56.5)	87.0	9.40	16.77	58.7%(G3：47.8%，G4：10.9%)
Zhao[71](2024)	回顾性单臂；FOLFOX-HAIC+仑伐替尼+durvalumab	iCCA	28	39.1(mRECIST 65.2)	82.6	11.9	17.9	46.5%
Zhang[72](2022)	回顾性双臂；HAIC(FOLFOX/GEMOX)+TKI+PD-1 vs ALT+TKI+PD-1	iCCA	39 vs 19	48.7 vs 15.8(RECIST)；61.5 vs 21.1(mRECIST)	82.1 vs 36.8	NR(1年PFS率61.9% vs 31.6%)	—	差异无统计学意义
Cai[74](2025)	回顾性双臂；HLP：HAIC+仑伐替尼+PD-1；SCLP：系统化疗+仑伐替尼+PD-1	iCCA	HLP：25 SCLP：28	52 vs 25	96.0 vs 78.6	8.8 vs 6.4	12.8 vs 11.0	HLP组≥G3~4 AE更少
Wei[75](2023)	回顾性；FOLFOX-HAIC+仑伐替尼±PD-1	CCA(mixed)	35 vs 20	28.60	80	6.5 vs 3.5	16 vs 11	无显著差异；PD-1组2例G5免疫相关肺炎
Li[76](2025)	多中心回顾性；(HAIC/TACE/RT)+仑伐替尼+ICI vs 化疗+ICI	iCCA	78 vs 70	51.3 vs 27.1	85.9 vs 81.4	10.8 vs 7.6	18.5 vs 15.0	60.3% vs 58.6%
Song[77](2025)	回顾性单臂；HAIC(mFOLFOX6)+托瑞帕利单抗+surufatinib	iCCA	28	57	79	9.5	—	21.42%
Lin[78](2024)	回顾性；FOLFOX-HAIC+仑伐替尼+PD-1 vs GC(吉西他滨/顺铂)	iCCA	51 vs 39(PSM 30/30)	43.1 vs 20.5	86.3 vs 66.7	12.0 vs 6.9	16.8 vs 11.0	系统化疗组AE较高
Hu[79](2025)	回顾性；PSM 40/40；动脉FOLFOX(HAIC)+PD-(L)1 vs 系统化疗+PD-(L)1	iCCA	182(PSM 61/26)	50.8 vs 26.9	91.8 vs 84.6	10.4 vs 6.4	14.5 vs 10.5	49.2% vs 46.2%
Li[80](2025)	多中心回顾性；LRT(HAIC/TACE/RT)+GEMOX(≥2周期)+仑伐替尼+ICI	iCCA	47	61.7	93.6	10.2	20.2	66.0%

注：HAIC，经导管肝动脉灌注化疗；iCCA，肝内胆管癌；ORR，客观缓解率；DCR，疾病控制率；PFS，无进展生存期；mOS，中位总生存期；AE，不良事件；PD-1，程序性死亡受体1；PD-L1，程序性死亡配体1；PSM，倾向评分匹配；TKI，酪氨酸激酶抑制剂；ICI，免疫检查点抑制剂；—，未报告。

10个月、OS为17个月，均高于对照组（8个月、11个月），且不良事件并未显著增加。此外，Huang等[82]对59例uiCCA患者实施TACE+PD-1抑制剂+Lenvatinib联合治疗，ORR为55.9%，DCR达96.6%，mPFS为9.5（95%*CI*：7.9～11.0）个月，mOS为25.8（95%*CI*：17.9～33.7）个月。治疗总体耐受性良好，但25.4%的患者出现3～4级不良事件；无治疗相关死亡或不可控制事件。然而，目前仍缺乏前瞻性及随机试验研究真实TACE联合靶向免疫的疗效。

截至目前，尚缺乏关于局部消融（如RFA、微波消融）或经动脉TARE联合靶向或免疫治疗用于iCCA的系统性临床研究或公开发表的可靠数据。现有文献多聚焦于局部治疗或系统治疗的单独应用，或将TARE与化疗联合使用的探索，极少研究涉及其与ICI（如PD-1/PD-L1）或靶向药物（如仑伐替尼、伊尼妥单抗）等系统性疗法的联合应用。与HCC相对丰富的相关研究相比，iCCA在该领域仍处于临床证据空白期。

4 小结与展望

iCCA是一种临床管理复杂、预后较差的恶性肿瘤。多数患者确诊时已失去手术机会，局部治疗（TACE、TARE、HAIC）已成为主要的治疗方式之一。近年来，局部治疗联合靶向及免疫治疗的综合策略逐渐受到关注。研究显示，该联合模式能够显著提高ORR，延长PFS和OS，部分患者甚至可以获得转化切除机会。目前，局部治疗联合靶向免疫治疗在iCCA中的研究重点主要包括以下几个方面：（1）不同局部治疗方式（如HAIC、TACE、TARE）与靶向药物及ICI的最优组合方案尚待明确；（2）联合治疗的时机与顺序仍存在争议，需探讨同步或序贯治疗模式的最佳选择；（3）疗效预测及个体化治疗亟须建立可靠的生物标志物体系，以筛选获益人群；（4）联合治疗的安全性与耐受性管理仍是临床实践中的关键问题；（5）现有研究多为小样本回顾性研究，缺乏大规模、多中心、随机对照试验支持，临床证据层级有限。总体来看，局部治疗联合靶向免疫治疗正逐渐成为uiCCA的重要治疗方向之一。随着临床研究的深入、治疗策略的优化及机制研究的完善，该联合模式有望进一步提高治疗效果，改善患者长期预后。

利益冲突声明：本文不存在任何利益冲突。

作者贡献声明：刘洋、施祥德负责设计并撰写论文；刘明奇负责对论文进行润色；刘超负责指导文章撰写并最后定稿。刘洋、施祥德对文章贡献等同，为共同第一作者。

参考文献：

[1] SIEGEL RL, MILLER KD, FUCHS HE, et al. Cancer statistics, 2022 [J]. CA A Cancer J Clin, 2022, 72(1): 7-33. DOI: 10.3322/caac.21708.
[2] BEAL EW, TUMIN D, MORIS D, et al. Cohort contributions to trends in the incidence and mortality of intrahepatic cholangiocarcinoma [J]. Hepatobiliary Surg Nutr, 2018, 7(4): 270-276. DOI: 10.21037/hbsn.2018.03.16.
[3] SAHA SK, ZHU AX, FUCHS CS, et al. Forty-year trends in cholangiocarcinoma incidence in the U.S.: Intrahepatic disease on the rise [J]. Oncologist, 2016, 21(5): 594-599. DOI: 10.1634/theoncologist.2015-0446.
[4] FLORIO AA, FERLAY J, ZNAOR A, et al. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012[J]. Cancer, 2020, 126(11): 2666-2678. DOI: 10.1002/cncr.32803.
[5] ENDO I, GONEN M, YOPP AC, et al. Intrahepatic cholangiocarcinoma: Rising frequency, improved survival, and determinants of outcome after resection[J]. Ann Surg, 2008, 248(1): 84-96. DOI: 10.1097/sla.0b013e318176c4d3.
[6] EL-DIWANY R, PAWLIK TM, EJAZ A. Intrahepatic cholangiocarcinoma[J]. Surg Oncol Clin N Am, 2019, 28(4): 587-599. DOI: 10.1016/j.soc.2019.06.002.
[7] MORIS D, PALTA M, KIM C, et al. Advances in the treatment of intrahepatic cholangiocarcinoma: An overview of the current and future therapeutic landscape for clinicians[J]. CA A Cancer J Clin, 2023, 73(2): 198-222. DOI: 10.3322/caac.21759.
[8] BENSON AB, D'ANGELICA MI, ABRAMS T, et al. NCCN Guidelines® Insights: Biliary tract cancers, version 2.2023[J]. J Natl Compr Canc Netw, 2023, 21(7): 694-704. 10.6004/jnccn.2023.0035.
[9] YUAN P, SONG JH, WANG F, et al. Combination of TACE and Lenvatinib as a promising option for downstaging to surgery of initially unresectable intrahepatic cholangiocarcinoma[J]. Investig New Drugs, 2022, 40(5): 1125-1132. DOI: 10.1007/s10637-022-01257-z.
[10] YANG XG, SUN YY, LI DS, et al. Efficacy and safety of drug-eluting beads transarterial chemoembolization combining immune checkpoint inhibitors in unresectable intrahepatic cholangiocarcinoma: A propensity score matching analysis[J]. Front Immunol, 2022, 13: 940009. DOI: 10.3389/fimmu.2022.940009.
[11] GEORGIADES CS, HONG K, GESCHWIND JF. Radiofrequency ablation and chemoembolization for hepatocellular carcinoma[J]. Cancer J, 2008, 14(2): 117-122. DOI: 10.1097/ppo.0b013e31816a0fac.
[12] KIEFER MV, ALBERT M, MCNALLY M, et al. Chemoembolization of intrahepatic cholangiocarcinoma with cisplatinum, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol: A 2-center study[J]. Cancer, 2011, 117(7): 1498-1505. DOI: 10.1002/cncr.25625.
[13] KIM JH, YOON HK, SUNG KB, et al. Transcatheter arterial chemoembolization or chemoinfusion for unresectable intrahepatic cholangiocarcinoma: Clinical efficacy and factors influencing outcomes [J]. Cancer, 2008, 113(7): 1614-1622. DOI: 10.1002/cncr.23787.
[14] VOGL TJ, NAGUIB NNN, NOUR-ELDIN NA, et al. Transarterial chemoembolization in the treatment of patients with unresectable cholangiocarcinoma: Results and prognostic factors governing treatment success[J]. Int J Cancer, 2012, 131(3): 733-740. DOI: 10.1002/ijc.26407.
[15] PARK SY, KIM JH, YOON HJ, et al. Transarterial chemoembolization versus supportive therapy in the palliative treatment of unresectable intrahepatic cholangiocarcinoma[J]. Clin Radiol, 2011, 66(4): 322-328. DOI: 10.1016/j.crad.2010.11.002.
[16] AYYUB J, DABHI KN, GOHIL NV, et al. Evaluation of the safety and efficacy of conventional transarterial chemoembolization (cTACE) and drug-eluting bead (DEB)-TACE in the management of unresectable hepatocellular carcinoma: A systematic review[J]. Cureus, 2023, 15(7): e41943. DOI: 10.7759/cureus.41943.
[17] TANG JJ, HUANG ZL, XU JC, et al. Drug-eluting bead transarterial chemoembolization (TACE) exhibits superior efficacy and equal tolerance to conventional TACE in hepatocellular carcinoma patients with conventional TACE history[J]. Clin Res Hepatol Gastroenterol, 2022, 46(3): 101814. DOI: 10.1016/j.clinre.2021.101814.
[18] KUHLMANN JB, EURINGER W, SPANGENBERG HC, et al. Treatment of unresectable cholangiocarcinoma: Conventional transarterial chemo-

embolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy[J]. Eur J Gastroenterol Hepatol, 2012, 24(4): 437-443. DOI: 10.1097/meg.0b013e3283502241.
[19] WANG JX, XUE YQ, LIU R, et al. DEB-TACE with irinotecan versus C-TACE for unresectable intrahepatic cholangiocarcinoma: A prospective clinical study[J]. Front Bioeng Biotechnol, 2023, 10: 1112500. DOI: 10.3389/fbioe.2022.1112500.
[20] SCHARTZ DA, PORTER M, SCHARTZ E, et al. Transarterial yttrium-90 radioembolization for unresectable intrahepatic cholangiocarcinoma: A systematic review and meta-analysis[J]. J Vasc Interv Radiol, 2022, 33(6): 679-686. DOI: 10.1016/j.jvir.2022.02.016.
[21] EDELINE J, LAMARCA A, MCNAMARA MG, et al. Locoregional therapies in patients with intrahepatic cholangiocarcinoma: A systematic review and pooled analysis[J]. Cancer Treat Rev, 2021, 99: 102258. DOI: 10.1016/j.ctrv.2021.102258.
[22] BOEHM LM, JAYAKRISHNAN TT, MIURA JT, et al. Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma: hepatic artery therapy for unresectable ICC[J]. J Surg Oncol, 2015, 111(2): 213-220. DOI: 10.1002/jso.23781.
[23] KEMENY NE, SCHWARTZ L, GÖNEN M, et al. Treating primary liver cancer with hepatic arterial infusion of floxuridine and dexamethasone: Does the addition of systemic bevacizumab improve results [J]. Oncology, 2011, 80(3-4): 153-159. DOI: 10.1159/000324704.
[24] CERCEK A, BOERNER T, TAN BR, et al. Assessment of hepatic arterial infusion of floxuridine in combination with systemic gemcitabine and oxaliplatin in patients with unresectable intrahepatic cholangiocarcinoma: A phase 2 clinical trial[J]. JAMA Oncol, 2020, 6(1): 60. DOI: 10.1001/jamaoncol.2019.3718.
[25] JARNAGIN WR, SCHWARTZ LH, GULTEKIN DH, et al. Regional chemotherapy for unresectable primary liver cancer: Results of a phase II clinical trial and assessment of DCE-MRI as a biomarker of survival[J]. Ann Oncol, 2009, 20(9): 1589-1595. DOI: 10.1093/annonc/mdp029.
[26] JOLISSAINT JS, SOARES KC, SEIER KP, et al. Intrahepatic cholangiocarcinoma with lymph node metastasis: Treatment-related outcomes and the role of tumor genomics in patient selection[J]. Clin Cancer Res, 2021, 27(14): 4101-4108. DOI: 10.1158/1078-0432.ccr-21-0412.
[27] CHIOU YY, HWANG JI, CHOU YH, et al. Percutaneous ultrasound-guided radiofrequency ablation of intrahepatic cholangiocarcinoma [J]. The Kaohsiung J Med Scie, 2005, 21(7): 304-309. DOI: 10.1016/s1607-551x(09)70125-1.
[28] MORIZANE C, OKUSAKA T, MIZUSAWA J, et al. Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: The FUGA-BT (JCOG1113) randomized phase III clinical trial[J]. Ann Oncol, 2019, 30(12): 1950-1958. DOI: 10.1093/annonc/mdz402.
[29] IOKA T, KANAI M, KOBAYASHI S, et al. Randomized phase III study of gemcitabine, cisplatin plus S-1 versus gemcitabine, cisplatin for advanced biliary tract cancer (KHBO1401- MITSUBA)[J]. J Hepato Biliary Pancreat, 2023, 30(1): 102-110. DOI: 10.1002/jhbp.1219.
[30] SHROFF RT, KING G, COLBY S, et al. SWOG S1815: A phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers[J]. J Clin Oncol, 2025, 43(5): 536-544. DOI: 10.1200/jco-24-01383.
[31] PHELIP JM, DESRAME J, EDELINE J, et al. Modified FOLFIRINOX versus CISGEM chemotherapy for patients with advanced biliary tract cancer (PRODIGE 38 AMEBICA): A randomized phase II study[J]. J Clin Oncol, 2022, 40(3): 262-271. DOI: 10.1200/jco.21.00679.
[32] AITCHESON G, MAHIPAL A, JOHN BV. Targeting FGFR in intrahepatic cholangiocarcinoma [iCCA]: Leading the way for precision medicine in biliary tract cancer [BTC]? [J]. Expert Opin Investig Drugs, 2021, 30(4): 463-477. DOI: 10.1080/13543784.2021.1900821.
[33] KENDRE G, MURUGESAN K, BRUMMER T, et al. Charting co-mutation patterns associated with actionable drivers in intrahepatic cholangiocarcinoma[J]. J Hepatol, 2023, 78(3): 614-626. DOI: 10.1016/j.jhep.2022.11.030.
[34] BABINA IS, TURNER NC. Advances and challenges in targeting FGFR signalling in cancer[J]. Nat Rev Cancer, 2017, 17(5): 318-332. DOI: 10.1038/nrc.2017.8.
[35] ABOU-ALFA GK, SAHAI V, HOLLEBECQUE A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: A multicentre, open-label, phase 2 study[J]. Lancet Oncol, 2020, 21(5): 671-684. DOI: 10.1016/s1470-2045(20)30109-1.
[36] VOGEL A, SAHAI V, HOLLEBECQUE A, et al. An open-label study of pemigatinib in cholangiocarcinoma: Final results from FIGHT-202 [J]. ESMO Open, 2024, 9(6): 103488. DOI: 10.1016/j. esmoop.2024.103488.
[37] RIZZO A, RICCI AD, BRANDI G. IDH inhibitors in advanced cholangiocarcinoma: Another arrow in the quiver?[J]. Cancer Treat Res Commun, 2021, 27: 100356. DOI: 10.1016/j.ctarc.2021.100356.
[38] LIN JZ, CAO YH, YANG X, et al. Mutational spectrum and precision oncology for biliary tract carcinoma[J]. Theranostics, 2021, 11 (10): 4585-4598. DOI: 10.7150/thno.56539.
[39] LAVACCHI D, CALIMAN E, ROSSI G, et al. Ivosidenib in IDH1-mutated cholangiocarcinoma: Clinical evaluation and future directions [J]. Pharmacol Ther, 2022, 237: 108170. DOI: 10.1016/j. pharmthera.2022.108170.
[40] ABOU-ALFA GK, MACARULLA T, JAVLE MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): A multicentre, randomised, double-blind, placebo-controlled, phase 3 study[J]. Lancet Oncol, 2020, 21(6): 796-807. DOI: 10.1016/s1470-2045(20)30157-1.
[41] ZHU AX, MACARULLA T, JAVLE MM, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with *IDH1* mutation: The phase 3 randomized clinical ClarIDHy trial[J]. JAMA Oncol, 2021, 7(11): 1669. DOI: 10.1001/jamaoncol.2021.3836.
[42] GALDY S, LAMARCA A, MCNAMARA MG, et al. HER2/HER3 pathway in biliary tract malignancies; systematic review and meta-analysis: A potential therapeutic target?[J]. Cancer Metastasis Rev, 2017, 36(1): 141-157. DOI: 10.1007/s10555-016-9645-x.
[43] PU XH, LI L, XU F, et al. HER2 amplification subtype intrahepatic cholangiocarcinoma exhibits high mutation burden and T cell exhaustion microenvironment[J]. J Cancer Res Clin Oncol, 2024, 150 (8): 403. DOI: 10.1007/s00432-024-05894-0.
[44] JAVLE M, BORAD MJ, AZAD NS, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): A multicentre, open-label, phase 2a, multiple basket study [J]. Lancet Oncol, 2021, 22(9): 1290-1300. DOI: 10.1016/s1470-2045(21)00336-3.
[45] KUDO M, FINN RS, QIN SK, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial[J]. Lancet, 2018, 391(10126): 1163-1173. DOI: 10.1016/s0140-6736(18)30207-1.
[46] ZHAO Y, ZHANG YN, WANG KT, et al. Lenvatinib for hepatocellular carcinoma: From preclinical mechanisms to anti-cancer therapy[J]. Biochim Biophys Acta BBA Rev Cancer, 2020, 1874(1): 188391. DOI: 10.1016/j.bbcan.2020.188391.
[47] SCHLUMBERGER M, TAHARA M, WIRTH LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer[J]. N Engl J Med, 2015, 372(7): 621-630. DOI: 10.1056/nejmoa1406470.
[48] UENO M, IKEDA M, SASAKI T, et al. Phase 2 study of lenvatinib monotherapy as second-line treatment in unresectable biliary tract cancer: Primary analysis results[J]. BMC Cancer, 2020, 20(1): 1105. DOI: 10.1186/s12885-020-07365-4.
[49] SHI GM, HUANG XY, WU D, et al. Toripalimab combined with lenvatinib and GEMOX is a promising regimen as first-line treatment for advanced intrahepatic cholangiocarcinoma: A single-center, single-arm, phase 2 study[J]. Sig Transduct Target Ther, 2023, 8: 106. DOI: 10.1038/s41392-023-01317-7.
[50] PIHA-PAUL SA, OH DY, UENO M, et al. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies[J]. Int J Cancer, 2020, 147(8): 2190-2198. DOI: 10.1002/ijc.33013.
[51] KIM RD, CHUNG V, ALESE OB, et al. A phase 2 multi-institutional study of nivolumab for patients with advanced refractory biliary tract cancer[J]. JAMA Oncol, 2020, 6(6): 888. DOI: 10.1001/jamaoncol.2020.0930.
[52] MELERO I, YAU T, KANG YK, et al. Nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma previously treated with sorafenib: 5-year results from CheckMate 040[J]. Ann Oncol, 2024, 35(6): 537-548. DOI: 10.1016/j.an-

nonc.2024.03.005.
[53] KLEIN O, KEE D, NAGRIAL A, et al. Evaluation of combination nivolumab and ipilimumab immunotherapy in patients with advanced biliary tract cancers: Subgroup analysis of a phase 2 nonrandomized clinical trial[J]. JAMA Oncol, 2020, 6(9): 1405. DOI: 10.1001/jamaoncol.2020.2814.
[54] SAHAI V, GRIFFITH KA, BEG MS, et al. A randomized phase 2 trial of nivolumab, gemcitabine, and cisplatin or nivolumab and ipilimumab in previously untreated advanced biliary cancer: BilT-01[J]. Cancer, 2022, 128(19): 3523-3530. DOI: 10.1002/cncr.34394.
[55] OH DY, RUTH HE A, QIN SK, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer[J]. NEJM Evid, 2022, 1(8): EVIDoa2200015. DOI: 10.1056/evidoa2200015.
[56] KELLEY R K, UENO M, YOO C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial[J]. Lancet, 2023, 401(10391): 1853-1865. DOI: 10.1016/s0140-6736(23)00727-4.
[57] ZHONG BY, FAN WZ, GUAN JJ, et al. Combination locoregional and systemic therapies in hepatocellular carcinoma[J]. Lancet Gastroenterol Hepatol, 2025, 10(4): 369-386. DOI: 10.1016/s2468-1253(24)00247-4.
[58] KIM DH. Combination of interventional oncology local therapies and immunotherapy for the treatment of hepatocellular carcinoma[J]. J Liver Cancer, 2022, 22(2): 93-102. DOI: 10.17998/jlc.2022.03.28.
[59] PINATO DJ, MURRAY SM, FORNER A, et al. Trans-arterial chemoembolization as a loco-regional inducer of immunogenic cell death in hepatocellular carcinoma: Implications for immunotherapy[J]. J Immunother Cancer, 2021, 9(9): e003311. DOI: 10.1136/jitc-2021-003311.
[60] TAKAKI H, IMAI N, CONTESSA TT, et al. Peripheral blood regulatory T-cell and type 1 helper T-cell population decrease after hepatic artery embolization[J]. J Vasc Interv Radiol, 2016, 27(10): 1561-1568. DOI: 10.1016/j.jvir.2016.01.150.
[61] HICKEY RM, KULIK LM, NIMEIRI H, et al. Immuno-oncology and its opportunities for interventional radiologists: Immune checkpoint inhibition and potential synergies with interventional oncology procedures[J]. J Vasc Interv Radiol, 2017, 28(11): 1487-1494. DOI: 10.1016/j.jvir.2017.07.018.
[62] LIU WM, FOWLER DW, SMITH P, et al. Pre-treatment with chemotherapy can enhance the antigenicity and immunogenicity of tumours by promoting adaptive immune responses[J]. Br J Cancer, 2010, 102(1): 115-123. DOI: 10.1038/sj.bjc.6605465.
[63] MEI ZB, GAO XX, PAN CX, et al. Lenvatinib enhances antitumor immunity by promoting the infiltration of $TCF1^{+}CD8^{+}$ T cells in HCC via blocking VEGFR2[J]. Cancer Sci, 2023, 114(4): 1284-1296. DOI: 10.1111/cas.15719.
[64] TORRENS L, MONTIRONI C, PUIGVEHÍ M, et al. Immunomodulatory effects of lenvatinib plus anti-programmed cell death protein 1 in mice and rationale for patient enrichment in hepatocellular carcinoma[J]. Hepatology, 2021, 74(5): 2652-2669. DOI: 10.1002/hep.32023.
[65] YAMAUCHI M, ONO A, AMIOKA K, et al. Lenvatinib activates antitumor immunity by suppressing immunoinhibitory infiltrates in the tumor microenvironment of advanced hepatocellular carcinoma[J]. Commun Med, 2023, 3: 152. DOI: 10.1038/s43856-023-00390-x.
[66] YANG JY, GUO ZX, SONG MJ, et al. Lenvatinib improves anti-PD-1 therapeutic efficacy by promoting vascular normalization via the NRP-1-PDGFRβ complex in hepatocellular carcinoma[J]. Front Immunol, 2023, 14: 1212577. DOI: 10.3389/fimmu.2023.1212577.
[67] LIN YS, LI S, YANG X, et al. First-line hepatic arterial infusion chemotherapy plus lenvatinib and PD-$(L)_1$ inhibitors versus systemic chemotherapy alone or with PD-$(L)_1$ inhibitors in unresectable intrahepatic cholangiocarcinoma[J]. J Cancer Res Clin Oncol, 2024, 150(6): 309. DOI: 10.1007/s00432-024-05795-2.
[68] XU QY, WANG CD, YOU R, et al. Hepatic arterial infusion chemotherapy (HAIC) plus Lenvatinib and PD-1 inhibitors versus systemic chemotherapy for unresectable intrahepatic cholangiocarcinoma[J]. Discov Oncol, 2025, 16(1): 775. DOI: 10.1007/s12672-025-02397-3.
[69] ZHENG ZK, WANG JL, WU TQ, et al. Hepatic arterial infusion chemotherapy plus targeted therapy and immunotherapy versus systemic chemotherapy for advanced intrahepatic cholangiocarcinoma: A retrospective cohort study[J]. Int J Surg, 2025, 111(1): 1552-1557. DOI: 10.1097/js9.0000000000002013.
[70] HUANG YX, DU ZF, KAN AN, et al. Clinical and biomarker analyses of hepatic arterial infusion chemotherapy plus lenvatinib and PD-1 inhibitor for patients with advanced intrahepatic cholangiocarcinoma[J]. Front Immunol, 2024, 15: 1260191. DOI: 10.3389/fimmu.2024.1260191.
[71] ZHAO RC, ZHOU J, MIAO ZX, et al. Efficacy and safety of lenvatinib plus durvalumab combined with hepatic arterial infusion chemotherapy for unresectable intrahepatic cholangiocarcinoma[J]. Front Immunol, 2024, 15: 1397827. DOI: 10.3389/fimmu.2024.1397827.
[72] ZHANG N, YU BR, WANG YX, et al. Clinical outcomes of hepatic arterial infusion chemotherapy combined with tyrosine kinase inhibitors and anti-PD-1 immunotherapy for unresectable intrahepatic cholangiocarcinoma[J]. J Dig Dis, 2022, 23(8-9): 535-545. DOI: 10.1111/1751-2980.13127.
[73] LI KS, ZHANG TZ, GAO Q, et al. HAIC plus TAE combined with tislelizumab and surufatinib in unresectable intrahepatic cholangiocarcinoma: The REACH-01 trial[J]. J Clin Oncol, 2025, 43(16_suppl): 4087. DOI: 10.1200/jco.2025.43.16_suppl.4087.
[74] CAI YX, WEN W, XIA YS, et al. The efficacy and safety of hepatic artery infusion chemotherapy combined with lenvatinib and programmed death (PD)-1 inhibitors for unresectable intrahepatic cholangiocarcinoma: A retrospective study[J]. Curr Oncol, 2025, 32(2): 87. DOI: 10.3390/curroncol32020087.
[75] WEI ZQ, WANG YJ, WU BY, et al. Hepatic arterial infusion chemotherapy plus lenvatinib with or without programmed cell death protein-1 inhibitors for advanced cholangiocarcinoma[J]. Front Immunol, 2023, 14: 1235724. DOI: 10.3389/fimmu.2023.1235724.
[76] LI SF, YU GH, WANG MM, et al. Local-regional therapy combined with immune checkpoint inhibitors and lenvatinib versus immune checkpoint inhibitors plus chemotherapy in advanced intrahepatic cholangiocarcinoma: A multicenter cohort study[J]. Cancer Immunol Immunother, 2025, 74(8): 271. DOI: 10.1007/s00262-025-04129-6.
[77] SONG SL, LIU YM, REN YQ, et al. Hepatic arterial infusion chemotherapy combined with toripalimab and surufatinib for the treatment of advanced intrahepatic cholangiocarcinoma[J]. Diagn Interv Radiol, 2025, 31(2):145-151. DOI: 10.4274/dir.2024.242673.
[78] LIN ZP, ZOU XG, HU XL, et al. Efficacy analysis of HAIC combined with lenvatinib plus PD-1 inhibitor vs. first-line systemic chemotherapy for advanced intrahepatic cholangiocarcinoma[J]. Sci Rep, 2024, 14: 23961. DOI: 10.1038/s41598-024-75102-z.
[79] HU Y, JIANG XY, CAI X, et al. Efficacy and safety of arterial FOLFOX chemotherapy plus anti-PD-$(L)_1$ immunotherapy as a first-line treatment for unresectable intrahepatic cholangiocarcinoma: A propensity score matching analysis[J]. J Gastrointest Oncol, 2025, 16(1): 209-225. DOI: 10.21037/jgo-24-552.
[80] LI SF, YU GH, WANG MM, et al. Efficacy and safety of local–regional therapy combined with chemotherapy, immune checkpoint inhibitors and lenvatinib as first-line treatment in advanced intrahepatic cholangiocarcinoma: A multicenter retrospective cohort study[J]. Cancer Immunol Immunother, 2025, 74(7): 229. DOI: 10.1007/s00262-025-04085-1.
[81] LIU S, WANG QD, YIN SH, et al. Efficacy analysis of drug-eluting beads transcatheter arterial chemoembolization combining systemic chemotherapy and immune checkpoint inhibitors in unresectable intrahepatic cholangiocarcinoma: A multicenter retrospective cohort study based on propensity score matching[J]. World J Surg Oncol, 2025, 23(1): 21. DOI: 10.1186/s12957-025-03679-4.
[82] HUANG JT, HU D, HONG X, et al. Effectiveness and safety of transarterial chemoembolization combined with PD-1 inhibitors and lenvatinib for unresectable intrahepatic cholangiocarcinoma[J]. Eur Radiol Exp, 2025, 9(1): 21. DOI: 10.1186/s41747-025-00563-4.

收稿日期：2025-10-27；**录用日期：**2025-11-20
本文编辑：王亚南

引证本文：LIU Y, SHI XD, LIU MQ, et al. Research advances in local treatment and systemic therapy for intrahepatic cholangiocarcinoma[J]. J Clin Hepatol, 2025, 41(12): 2453-2461.
刘洋, 施祥德, 刘明奇, 等. 肝内胆管癌局部治疗及系统治疗研究进展[J]. 临床肝胆病杂志, 2025, 41(12): 2453-2461.