·专 论 Special comment·

肝内胆管癌介入治疗研究进展

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【摘要】 肝内胆管癌(iCCA)发病隐匿且侵袭性强，绝大多数患者确诊时已处于中晚期，预后较差。中晚期 iCCA 治疗主要包括系统治疗和局部治疗，但单一疗法疗效有限。近来研究表明，以消融治疗、经导管动脉化疗栓塞(TACE)、经导管动脉放疗栓塞(TARE)、肝动脉灌注化疗(HAIC)^{125}I 放射性粒子植入等介入手段为基础的综合治疗策略，可显著改善中晚期 iCCA 患者生存率，同时有效减少不良事件发生。该文综述 iCCA 介入治疗研究进展。

【关键词】 肝内胆管癌；局部治疗；介入；靶向治疗；免疫治疗

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Progress in interventional treatment of intrahepatic cholangiocarcinoma

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【Abstract】 Clinically, intrahepatic cholangiocarcinoma (iCCA) is characterized by insidious onset and strong invasiveness. The vast majority of iCCA patients have already been in the middle and advanced stage of disease when the diagnosis is confirmed, and the prognosis is poorer. The therapeutic methods for the middle and advanced iCCA mainly consist of systemic therapy and local therapy. However, the efficacy of single-agent therapies is limited. Recent studies have demonstrated that comprehensive treatment strategies based on interventional approaches, such as ablation, transarterial chemoembolization (TACE), transcatheter radioembolization (TARE), hepatic arterial infusion chemotherapy (HAIC), and iodine-125 (^{125}I) seeds implantation can significantly improve survival rate for patients with middle and advanced iCCA, meanwhile effectively reducing the incidence of adverse events. This article aims to review the latest progress in the interventional treatment for iCCA.

【Key words】 intrahepatic cholangiocarcinoma; local therapy; intervention; targeted therapy; immunotherapy

肝内胆管癌(intrahepatic cholangiocarcinoma，iCCA)是一种原发性肝脏恶性肿瘤，占所有肝脏恶性肿瘤 10%～15%[1-2]。iCCA 发病隐匿、进展迅速，确诊时往往已处于中晚期[3]。对于不可切除的肝内胆管癌(unresectable iCCA，uiCCA)，系统治疗和局部治疗是主要治疗方法。其中系统治疗是 70%～80% uiCCA 患者护理的关键组成部分[4]。最新美国国立综合癌症网络(National Comprehensive Cancer Network，NCCN)指南[5]推荐将吉西他滨和顺铂(GemCis)联合度伐利尤或帕博利珠作为 uiCCA 一线化疗方案。然而单纯药物治疗临床效益有限且不良事件发生率较高，严重影响患者生存质量[6-7]。近年以消融治疗、经导管动脉化疗栓塞(TACE)、经导管动脉放疗栓塞(transareterial radioembolization，TARE)、肝动脉灌注化疗(hepatic arterial infusion chemotherapy，HAIC)及^{125}I 粒子植入等介入手段为基础，结合化疗、靶向治疗和(或)免疫治疗的综合治疗方案，在中晚期 iCCA 患者中展现出良好疗效。合理的联合治疗策略能够显著改善 iCCA 患者总生存期(overall

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survival, OS）和无进展生存期（progression-free survival, PFS），并有效控制不良事件[8-10]。本文就中晚期 iCCA 介入综合治疗方案的最新研究进展作一综述。

1　肿瘤消融

肿瘤消融是指直接将化学物质或热能作用于肿瘤局部，以达到根治或破坏实体肿瘤的目的[11]。射频消融（radiofrequency ablation, RFA）和微波消融（microwave ablation, MWA）是目前 iCCA 最常用的两种消融治疗方法[10]。RFA 与 MWA 疗效相似，均可作为早期或术后复发性 iCCA 手术切除的优选方案[12-14]。单纯消融治疗主要适用于肿瘤直径＜3 cm、肿瘤数＜3 枚的 iCCA 患者[14-15]。目前尚缺乏 iCCA 消融治疗的前瞻性临床试验研究，但回顾性研究显示了其安全性和有效性[16-17]。一项纳入 917 例患者的系统回顾和 Meta 分析显示，消融治疗技术成功率为 91.9%，1、3、5 年患者 OS 率分别为 82.4%、42.1%、28.5%，严重并发症发生率为 5.7%[16]。

对于 uiCCA 患者，消融治疗也展示出良好的应用前景。近来研究发现，系统化疗联合消融治疗较单纯系统化疗可显著提高患者 OS，且不增加治疗相关不良事件。孙巍等[18]回顾性分析了 RFA 联合系统化疗（GemCis）对复发性 iCCA 的疗效，结果显示该方案客观缓解率（objective response rate, ORR）为 79.2%，术后 1 个月肿瘤完全消融率为 86.7%，中位 OS 为 28.6 个月。魏春等[19]对比了 MWA 联合系统化疗（以吉西他滨为基础）与单纯 MWA 治疗复发性 iCCA 的效果和安全性，结果显示 MWA 联合系统化疗组中位 PFS 为 15.0 个月，显著高于单纯 MWA 组 13.4 个月，中位 OS 分别为 21.0 个月、18.0 个月，两组间不良事件发生率差异无统计学意义。Yan 等[20]研究显示，接受消融联合系统化疗（以吉西他滨为基础）的 uiCCA 患者中位 OS 显著高于单纯系统化疗患者（16.3 个月比 6.1 个月），倾向性评分匹配分析进一步验证了这一生存优势（15.2 个月比 8.0 个月），表明治疗方式是影响 OS 的独立因素。此外，有研究显示，消融治疗会对肿瘤免疫微环境产生积极影响[21]。这表明肿瘤消融联合免疫治疗是 iCCA 治疗的潜在研究方向，但目前尚缺乏该领域相关临床试验研究。

肿瘤消融具有微创、患者恢复快和并发症较少的优点。但其临床应用受到肿瘤数量、大小和解剖位置的限制，且治疗后局部残余肿瘤进展率相对较高[22]，对中晚期 iCCA 临床效益有限。此外，接受肿瘤消融的初诊患者多缺乏 iCCA 组织病理学诊断，且无法进行淋巴结清扫，后者会影响早期 iCCA 根治性[23]。

2　TACE

根据栓塞剂不同，TACE 分为常规 TACE（conventional TACE, cTACE）和药物洗脱微球 TACE（drug-eluting beads TACE, DEB-TACE）[24]。cTACE 是指将化疗药物单独或与碘化油混悬后与明胶海绵、聚乙烯醇或校准微球等颗粒同时（组成化疗栓塞乳剂），或按先后顺序分别进行栓塞[25]。cTACE 在使用碘化油或明胶海绵等材料进行栓塞时可能会对肝功能造成损害。DEB-TACE 将化疗药物加载或吸附至微球，以实现体内持续释放药物[25]。DEB-TACE 通过采用新型药物释放微球（如 CalliSpheres）进行栓塞，能有效降低肝损伤风险。TACE 治疗原理基于正常肝脏与恶性肿瘤的血供差异。正常肝脏 75%血供来自门静脉、25%血供来自肝动脉，而肝脏恶性肿瘤则主要由肝动脉供血[26]。iCCA 血供特点遵循上述原则，且肿瘤组织无 Kupffer 细胞，缺乏吞噬能力，这些特征有利于栓塞剂在肿瘤局部积聚。由于 iCCA 血管化程度相对较低，相较于 cTACE，DEB-TACE 术时采用微球能达到更精细的栓塞和更好的局部药物释放效果，使其逐渐成为 iCCA 治疗的重要选择[27]。研究表明，DEB-TACE 在 uiCCA 治疗中中位 OS、疾病控制率（disease control rate, DCR）及 ORR 均优于 cTACE[27-29]。

近年来，TACE 作为局部治疗手段在 iCCA 中的应用逐渐增加，其与系统化疗联合应用展现出良好疗效[30-33]。Martin 等[30]报道一前瞻性多中心、开放标签的随机Ⅱ期临床试验研究，结果显示接受 DEB-TACE 联合 GemCis 系统化疗的 uiCCA 患者中位 PFS、OS 均显著高于单纯系统化疗患者（PFS 31.9 个月比 10.1 个月，OS 33.7 个月比 12.6 个月）。Jiang 等[31]多中心回顾性队列研究同样显示，TACE 联合系统化疗（主要为 GemCis）中位 OS、DCR、ORR 均显著优于单独系统化疗。

TACE 联合靶向治疗同样展现出可观的疗效。一项回顾性研究对比了阿帕替尼联合 DEB-TACE、阿帕替尼联合 cTACE 与单纯阿帕替尼在 uiCCA 患者中的疗效和安全性，结果显示阿帕替尼联合 DEB-TACE 组 ORR、DCR 最高（ORR 84.6%，DCR

100%),其次是阿帕替尼联合 cTACE 组(ORR 75.0%,DCR 91.7%),而单纯阿帕替尼组最低(ORR 40.0%,DCR 80.0%)。尽管阿帕替尼联合 DEB-TACE 组及阿帕替尼联合 cTACE 组不良事件发生率高于单纯阿帕替尼组,但其不良事件均在可接受范围内[34]。另一项针对 44 例接受 TACE 联合仑伐替尼治疗的初诊 uiCCA 患者研究,结果显示有 28 例(63.6%)成功降期获得手术切除[35]。

免疫检查点抑制剂(immune checkpoint inhibitor,ICI)是一类免疫肿瘤治疗药物,通过增强宿主免疫系统消除癌细胞,从而产生抗肿瘤效果[36],近年在晚期癌症治疗中逐渐受到重视[37-38]。一项回顾性研究结果显示,DEB-TACE 联合 ICI 治疗 uiCCA 患者 ORR 显著高于单纯 GemCis 系统化疗(55.0%比 20.0%,$P=0.022$),中位 PFS(7.2 个月比 5.7 个月,$P=0.036$)、OS(13.2 个月比 7.6 个月,$P=0.015$)也明显优于系统化疗,且两者间治疗相关不良事件比较差异均无统计学意义[39]。

TACE 联合靶向免疫治疗也已应用于 uiCCA 治疗。近年一项研究评估了 TACE 联合仑伐替尼及程序性细胞死亡蛋白(programmed death,PD)-1 抑制剂对 uiCCA 的疗效,结果显示中位 OS 为 25.3 个月,中位 PFS 为 7.3 个月,DCR 达 71.9%;尽管 81.3%患者经历了不良事件,但大多为轻至中度(71.8%为 1～2 级)[40]。目前关于 TACE 联合靶向免疫治疗 uiCCA 前瞻性研究仍不足,需要更多随机对照试验和大规模临床研究进一步验证其广泛适用性及长期疗效。

3　TARE

TARE 又称选择性内放疗(selective internal radiotherapy,SIRT),是指将放射性物质如^{131}I 标记的碘油或含^{90}Y 等类似物微球注入肝动脉[25]。微球优先输送至肿瘤部位,并选择性地向肿瘤释放高能、低穿透性射线。目前最常用的是^{90}Y(一种 β 放射性同位素)树脂或玻璃微球[41]。TARE 适用于伴有门静脉栓塞 iCCA 患者,而门静脉栓塞通常被视为手术、肝移植和 TACE 禁忌证[42]。目前已有多项研究评估了 TARE 在 uiCCA 治疗中的有效性和安全性[43-45]。Cocozza 等[46] Meta 分析显示,接受 TARE 治疗的 uiCCA 患者 1、2、3 年 OS 率分别为 52.6%、27%、16.8%,其中初治患者显示出更高的 OS(中位 OS 19.7 个月)。另一项 2023 年前瞻性研究针对 24 例仅接受 TARE 治疗 uiCCA 患者,结果显示中位 PFS 为 5.5 个月,OS 为 19.4 个月,仅 2 例(8%)有 3 级不良反应[47]。值得注意的是,TARE 治疗 uiCCA 患者 OS 与一线系统化疗相比相似,但其不良事件发生率更低[45-48]。

近年来,TARE 与系统化疗的联合应用备受关注。Cucchetti 等[49] Meta 分析表明,TARE 更适用于肿块型 iCCA 患者(对比浸润型 iCCA,中位 OS 为 20 个月比 8 个月)、同步系统治疗患者(对比单纯 TARE 治疗,中位 OS 为 20 个月比 6 个月)以及初诊患者(对比既往治疗者,中位 OS 为 24 个月比 12 个月);后续研究进一步验证了这一结论。一项多中心Ⅱ期临床试验(MISPHEC)研究针对 41 例接受 TARE 联合 GemCis 系统化疗的 uiCCA 患者,结果显示 3 个月时 ORR 为 39%,DCR 高达 98%,中位 PFS、OS 分别为 22 个月、14 个月,其中 22%患者降期实现了肿瘤 R0 切除[50]。目前该研究的Ⅲ期临床试验正在进行[51]。另一回顾性研究针对 13 例接受 TARE 联合系统性吉西他滨、顺铂和卡培他滨治疗的初治 uiCCA 患者,结果显示 1、2 年 OS 率分别为 84.6%、52.9%,53.8%患者实现了降期切除[52]。

TARE 在 iCCA 治疗中展现出广阔前景,但其疗效受肿瘤大小及血供情况限制,对多发性肿瘤的控制效果较差且对技术和设备要求较高。随着更多临床研究开展,有望进一步确认其有效性和安全性,并探索其联合治疗策略,为患者带来更多治疗选择。

4　HAIC

HAIC 是一种采用外科或介入方式于动脉内置入导管并经导管向肝脏内灌注化疗药物,从而达到治疗肝恶性肿瘤的技术[53]。HAIC 治疗 iCCA 原理同样取决于肝恶性肿瘤血供特性,但与 TACE 不同的是,其可直接将高浓度化疗药物灌注至肿瘤局部,无需进行栓塞,因此治疗效果不受 iCCA 乏血供特性限制。

研究表明,相较于系统化疗,HAIC 对 uiCCA 具有更好疗效[54-56]。Franssen 等[54]研究结果显示,HAIC 组、GemCis 系统化疗组中位 OS 分别为 27.7 个月、11.8 个月;3 年 OS 率分别为 34.3%、3.5%,相差近 10 倍。另有研究表明,HAIC 在多灶性或伴有淋巴结转移的 iCCA 患者中的 OS 与手术切除相似,且均显著高于系统治疗[57-58]。对于这些患者,HAIC 有望替代手术切除。

多项国内外研究显示,HAIC 联合系统化疗对

uiCCA 具有显著疗效[59-65]。Cercek 等[60]报道Ⅱ期单臂临床研究对 38 例 uiCCA 患者进行氟尿苷-HAIC 联合吉西他滨和奥沙利铂治疗，其中 92%为初治，66%呈多灶性病变，47%伴有淋巴结转移，结果显示中位 PFS、OS 分别为 11.8 个月、25 个月，DCR 达到 84%，有 4 例患者(11%)降期获得手术切除。为进一步验证该方案有效性，另一多中心随机临床试验(NCT04891289)研究正在进行。此外，研究表明，HAIC 联合系统化疗与单纯系统化疗相比，因肝功能衰竭所致死亡率显著降低(42%比 72%，$P=0.002$)[61]。

近年以介入手段为基础结合靶免治疗的联合疗法，已成为 uiCCA 治疗领域研究热点。多项研究显示，以 HAIC 为基础的联合方案相较于其他方案具有显著优势[66-68]。Zhang 等[66]研究比较了 HAIC 或 TACE 联合酪氨酸激酶抑制剂(tyrosine kinase inhibitor，TKI)和抗 PD-1 免疫治疗在 uiCCA 中的疗效和安全性，58 例纳入患者中 39 例接受 HAIC 联合治疗(HTP 组)，19 例接受 TACE 联合治疗(TTP 组)，结果显示 HTP 组 ORR、DCR 均显著高于 TTP 组(ORR 按 RECIST 和 mRECIST 标准分别为 61.5%比 48.7%和 21.1%比 15.8%，DCR 为 82.1%比 36.8%)；尽管 HTP 组出现了更多皮疹、腹痛和手足综合征等不良事件，但对症治疗后均得到缓解，未出现治疗相关死亡。

多项研究评估了 HAIC 联合疗法的初步疗效和安全性[69-73]。近期一项研究显示，与系统化疗(GemCis 或吉西他滨联合奥沙利铂)相比，HAIC 联合靶向治疗和免疫治疗显著提高了 uiCCA 患者中位 OS(20.77 个月比 14.83 个月，$P=0.047$)、FPS(9.07 个月比 6.23 个月，$P<0.001$)及 ORR(35.5%比 14.5%，$P=0.003$)[69]。其他研究采取不同的靶向和免疫药物组合，亦取得了良好效果(中位 PFS 为 9.4～30.0 个月，OS 为 11.3～19.5 个月)[71-77]。本中心对 uiCCA 患者应用 HAIC 联合靶向治疗和免疫治疗方案——mFOLFOX6-HAIC(奥沙利铂第 1 天 85 mg/m^2，持续 2 h；亚叶酸钙第 1 天 200 mg/m^2，持续 2 h；5-氟尿嘧啶第 1 天静脉推注 400 mg/m^2，之后持续输注 46 h 至 2 400 mg/m^2；每 3 周进行 1 次)联合特瑞普利(静脉注射，每 3 周 240 mg)和索凡替尼(口服，每日 150 mg)，也取得了良好的临床疗效(ORR 为 58%，DCR 为 79%，中位 PFS 为 9.5 个月，OS 率为 83.3%)[72]。基于以上结果，本中心目前正在进行相同方案的Ⅱ期临床研究。

单纯 HAIC 治疗存在耐药性挑战，而以 HAIC 为基础的联合疗法在多个回顾性研究中表现出良好潜力，但目前仍缺乏系统的前瞻性研究和大规模随机多中心研究数据验证其可靠性和普遍适用性。山东大学一项名为“REACH-01”单臂、开放标签前瞻性研究(NCT06239532)，旨在探讨 HAIC 序贯经导管动脉栓塞联合替雷利珠和索凡替尼对 uiCCA 患者的疗效，目前正在进行中[78]。未来研究应继续探索 HAIC 最佳联合策略，以期为 uiCCA 患者提供更加有效的治疗方案。

5　^{125}I 粒子植入

^{125}I 粒子植入治疗是一种近距离放射治疗技术，通过影像引导或外科手术将^{125}I 粒子植入肿瘤局部后持续性发射半衰期为 59.6 d、杀伤距离为 1.7 cm 的 γ 射线，从而近距离持续杀伤周边肿瘤细胞，且对邻近正常组织损伤小[79]。目前该技术已应用于治疗包括 iCCA 在内多种晚期恶性肿瘤。研究显示，^{125}I 粒子放射性粒子可通过诱导 ROS/p53 信号通路活化，同时使 VEGFR2/PI3K/AKT 通路失活，从而抑制胆管癌(CCA)细胞增殖、迁移和侵袭，并促进凋亡[80-82]。

目前单纯^{125}I 放射性粒子植入治疗 iCCA 的文献报道较少。一项针对仅接受^{125}I 粒子植入治疗的不可切除或局部复发的 iCCA 患者研究显示，患者中位局部 PFS 为 4.6 个月(95%CI=2.3～7.0 个月)，1 年 OS 率为 53.5%[83]。另一研究纳入了 11 例接受^{125}I 粒子治疗的 iCCA 患者，其中 1 例达到完全缓解，6 例部分缓解，中位 OS 为 10 个月[84]。

有研究比较了^{125}I 粒子支架植入联合 TACE 与单纯^{125}I 粒子支架植入对 CCA 的疗效，结果显示联合治疗在降低 CCA 患者肿瘤标记物及 p53 水平、减少肿瘤病灶、提高患者生存率方面具有显著优势[85]。此外，张贵军等[86]比较了^{125}I 放射性粒子植入联合 RFA 治疗与系统化疗(GemCis)对中晚期 iCCA 患者的疗效，结果显示联合治疗组 ORR 明显高于系统化疗组(70.83%比 37.50%，$P<0.05$)。

恶性梗阻性黄疸(malignant obstructive jaundice，MOJ)是 iCCA 常见并发症，目前常用治疗方法包括经皮肝穿刺胆道引流术和胆道支架植入术。近年多项研究显示，^{125}I 放射性粒子植入在 MOJ 治疗中表现出良好的临床效益[87-90]。一项前瞻性非随机对照临床研究比较了仅进行胆道支架植

入与联合^{125}I 粒子条植入对 CCA 伴 MOJ 患者的疗效和安全性,结果显示联合组支架中位通畅时间和 DCR 均显著高于对照组[87]。柴杰等[88]研究也显示出相似结果,经皮胆道^{125}I 粒子支架植入组、单纯胆道金属裸支架植入组胆道通畅时间分别为(8.93±3.28)个月、(6.59±3.14)个月,术后 OS 分别为(12.12±6.28)个月、(9.02±4.12)个月,差异均有统计学意义。此外,有研究探讨了影响 MOJ 患者胆道支架植入联合^{125}I 粒子条内放射治疗预后的因素,发现淋巴细胞、调节性 T 细胞(regulatory T cells,Treg)是 OS 独立危险因素;淋巴细胞≥0.237 或 Treg≥0.21 的 MOJ 患者接受胆道支架植入联合^{125}I 粒子条内放射治疗,可能获得更长 OS[91]。

^{125}I 放射性粒子植入具有安全、精准、微创、可重复等优点,是有效的 iCCA 局部治疗方法,但目前仍缺乏相关指南和大规模临床试验予以规范治疗流程和验证长期疗效。

6　展望

iCCA 侵袭性极强,预后不佳。近年来介入治疗在 iCCA 中的应用不断发展,为患者提供了新治疗选择。将介入治疗与靶向治疗和免疫治疗相结合的综合策略展现出良好前景,现有临床研究已显示出可观的疗效。然而,仍需通过更多大规模临床试验研究验证综合治疗方案的长期效果和安全性。理想的治疗方案应根据患者具体病理特征和治疗反应进行相应调整,合理整合多种手段,以显著提升 iCCA 患者生存率和生活质量。

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