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肝内胆管癌的综合治疗

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摘　要　肝内胆管癌（ICC）具有恶性程度高，发现晚，容易发生淋巴结转移、脉管侵润及肝内播散等特点，导致患者预后较差。根治性手术仍然是目前唯一可以使患者获得长期生存的治疗方式，但存在根治性切除率低、术后容易复发等诸多难题以及肝切除范围和切缘宽度确定、淋巴结清扫与否等诸多争议。辅助治疗是综合治疗的重要组成部分，但放化疗尚无规范、有效的方案，靶向治疗与免疫治疗正处于临床探索阶段。随着分子生物学技术的进展，发现 ICC 在基因突变、信号传导以及临床病理特征上展现出高度的异质性。笔者从 ICC 生物学特性及临床特点的异质性出发，结合 ICC 治疗策略和新的综合治疗理念，为其个体化治疗提供新的思路与研究方向。

关键词　胆管肿瘤；胆管，肝内；异质性；肿瘤治疗方案
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Multimodality treatment of intrahepatic cholangiocarcinoma

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Abstract　Intrahepatic cholangiocarcinoma (ICC) is characterized by highly malignant behavior, being difficult to make an early detection, and frequent lymph node metastasis, vascular invasion and intrahepatic dissemination, which lead to the poor prognosis of the patients. At present, radical operation is still the only therapy for providing a chance of long-term survival, but it faces many problems such as low radical-resection rate and high postoperative recurrence rate, as well as many controversies such as determinations for the scope of liver resection and the width of the surgical margin and whether the lymph node dissection should be done. Adjuvant therapy is a critical component of the multimodality treatment, but there are no standard directions and effective protocols for its chemoradiotherapy, and the targeted therapy and immunotherapy are at the stage of exploration. With the development of molecular biological techniques, high degree of heterogeneity has been found in ICC in terms of gene mutation, signal transduction and clinicopathologic features. Here, the authors from the heterogeneity of the biological characteristics and clinical features of ICC in combination with the treatment strategies and the new concept of integrated therapy for ICC, provide new insights and research directions for its individualized treatment.

肝内胆管癌（intrahepatic cholangiocarcinoma，ICC）是指位于肝内二级及以上胆管上皮来源的恶性肿瘤[1]，也称肝内胆管细胞癌（intrahepatic cholangiocellular carcinoma，ICC），是仅次于肝细胞肝癌（hepatocellular carcinoma，HCC）的肝脏恶性肿瘤。ICC发病率近20年来在世界范围内呈显著上升趋势[2-3]。随着外科技术的不断改进，ICC根治性切除率得到提高，但其术后长期生存率并没有得到明显改善，在大多数研究中ICC术后5年生存率仅为25%~35%[3-5]。外科手术作为ICC最有效的治疗方式，目前尚存在包括肝切除范围、切缘距离、淋巴结清扫等诸多重要环节的争议，且辅助治疗尚无明确规范的治疗方案。极差的预后与治疗争议提示着外科医生对ICC的理解存在盲区，也提示着治疗理念与模式需要改进。研究[6-7]发现，ICC在致病因素、地域分布、临床表现、生物学特征、细胞起源以及分化等方面存在较大异质性。新的理念提示，恶性肿瘤是一个全身性系统性疾病，需要全身治疗而不是单纯的局部切除，需要序贯治疗而不是一个阶段性的治疗。本文从ICC生物学特性及临床特点的异质性出发，结合ICC治疗争议和新的综合治疗理念，为ICC的个体化综合治疗提供新的思路与研究方向。

1 手术治疗

1.1 肝切除术

根治性切除是目前得到广泛认可的ICC首选治疗方式，包括肿瘤的完全切除，切缘阴性，同时能保留足够肝组织（剩余至少两个连续肝段，且具有充分血流灌注，静脉回流和胆汁引流）。术前需要准确评估其手术切除的安全性和有效性，在尽量达到R0切除的前提下，同时考虑残余肝脏能否有效代偿的安全性问题。美国肝胆胰协会2015版ICC诊治专家共识将远处转移、超出区域淋巴结转移如腹主动脉旁淋巴结转移、双侧肝内多发病灶或多中心病灶视为手术禁忌证[8]。肝切除的范围与手术切缘尚无统一意见。具体切除范围根据病灶位置、大小和器官侵犯情况而定。术中为了获得根治性切除，可能倾向于切除更多的肝

脏。但Zhang等[9]研究指出，大范围肝切除对术后整体生存率并无获益，却会增加围手术期并发症的发生。该研究进一步指出，切缘宽度，而不是切除范围，影响长期生存结果，如果能实现切缘宽度≥5 mm，应提倡保留肝实质的根治性切除。也有研究[10]指出，切缘>10 mm可延长患者术后生存期，手术切缘宽度越小其复发的风险越高。目前已普遍认识到R0切除对ICC根治的重要性，R0切除通常定义为完整切除大体可见肿瘤及切缘阴性，但各中心报道的R0切除率差异较大，可能的原因包括肿瘤分期、手术方式和手术水平，而R0本身定义也尚为完全统一[11-12]。中国抗癌协会ICC诊治指南提出，R0切除肿瘤距切缘至少5~10 mm[13]。综上，ICC肝切除术在肝切除范围、切缘宽度以及R0准确定义上均尚未完全统一，立足具体病例，根据ICC不同临床病理类型选择合适的切除范围成为外科医生首要考虑。

1.2 淋巴结清扫

ICC具有高度恶性的生物学行为，淋巴转移发生早。据报道，ICC淋巴转移率可达30%~65%[14-17]。肝内胆管癌的淋巴播散主要沿如下3条途径[13]：(1) 通过肝十二指肠韧带；(2) 通过贲门旁、胃小弯及胃左动脉；(3) 通过膈下动脉或直接从右肝到主动脉旁的外侧组。ICC是否常规行淋巴结清扫以及清扫范围均存在较大争议。较大宗病例研究[17-18]指出，肝门部淋巴结清扫对ICC患者并无明显生存获益，但其有助于获得准确的肿瘤分期，可为手术后或无法根治性切除的患者行辅助治疗提供分期依据，建议常规行肝门淋巴结清扫术。而Miyata等[19]发现，无论肝门部淋巴结有无转移，清扫组和未清扫组在术后生存期和无复发生存期上差异无统计学意义，并建议临床实践中严格把控肝门部淋巴结清扫的指征，不建议常规执行清扫。类似报道[20]指出在没有区域淋巴结转移的情况下，ICC患者不会受益于淋巴结清扫术。然而，如已明确淋巴转移的位置，系统性淋巴结切除术可以改善ICC预后，建议严格选择病例行淋巴结清扫。尚有报道[21]指出，以性别、年龄或肿瘤大小区分的特定亚组可从淋巴结清扫中获益，如60岁以下的肿块型ICC可从淋巴结清扫中获益。国内学者[22]回顾性

研究分析190例ICC患者临床病理资料，对比评估CT、MRI、PET-CT在ICC临床分期中的价值，结果发现PET-CT在检测区域淋巴结转移的准确率和灵敏度分别为86.7%和80.0%，检测远处转移的准确率为98.42%，与CT、MRI相比差异均有统计学意义。PET-CT检查弥补了CT和MRI检查诊断ICC分期中区域淋巴结转移和远处转移的不足，有助于术前明确淋巴结转移情况，决定术中是否行淋巴结清扫术。综上，ICC患者能否从淋巴结清扫中获益涉及淋巴结具体转移部位、肿瘤类型、患者一般情况等因素，是否行淋巴结清扫需结合患者具体情况决定。

1.3　ICC 异质性与肝切除、淋巴结清扫

　　ICC在致病因素、地域分布、临床表现、生物学特征等方面存在较大异质性。近年来的研究[23]发现，ICC的细胞起源呈多元化，包括肝细胞、胆管上皮细胞、管周腺体细胞和肝干细胞等，同时其发生、发展及转移等与糖代谢、脂代谢等多种代谢密切相关[24]，提示ICC的生物学特征、临床表现的异质性可能与其多元化细胞起源、多种代谢机制及途径密切相关[7]。笔者团队[25]曾研究报道的国内首个ICC临床异质性及淋巴结转移多中心大样本（1 321例）临床研究，就ICC发病因素与肿瘤原发位置、淋巴结转移高危因素等得出重要结论。同时就ICC细胞起源总结了最新的实验证据和相关文献，以提供ICC细胞起源的最新观点，帮助建立ICC发生的分层模型，改进ICC基于解剖学的分类标准[6]。

　　日本肝癌研究协会（LCSGJ）[26]将ICC分为3种大体类型：肿块型（mass-forming type，MF）、管周浸润型（periductal infiltrating type，PI）和管内生长型（intraductal growth type，IG）。Shimada等[27]指出，MF+PI型ICC与黄疸、胆管侵犯、门静脉侵犯、淋巴结侵犯及肿瘤切缘阳性密切相关，其复发率高于其他类型的ICC，预后更差。ICC的大体分型与淋巴结转移发生率相关（IG：MF：MF+PI：PI=0：16%：50%：66%）[28]。Suzuki等[29]研究发现，MF型和MF+PI型ICC的5年生存率分别为47%和0。

　　通过前期关于ICC细胞起源的基础研究与ICC临床特点与淋巴结转移的临床研究，结合日本LCSGJ的大体病理分类（肿块型、管周浸润型、肝内生长型），笔者认为起源于肝细胞的ICC大体表现为MF型，其生物学特性与HCC类似；管周腺体细胞来源的ICC则表现为PI型，可沿门静脉系统周围的淋巴、神经转移，侵袭性较强，易造成早期淋巴结转移及神经侵犯，预后较差；起源于胆管上皮细胞的ICC表现为IG型，恶性程度低，沿管壁环形生长，恶性程度相对最低，预后较好；而MF+PI型ICC可能与肝前体细胞、肝干细胞起源有关，恶性转化能力强，恶性程度最高。术前通过影像学检查大多能够明确ICC分型，而相应的外科治疗方式是否可根据分型进行相应调整，如：MF型ICC治疗策略参照原发性肝细胞癌，淋巴结不做常规清扫，如术前术中怀疑，则行淋巴结清扫；PI型和MF+PI型ICC的治疗应尽量在解剖性肝切除的基础上，扩大肝切除范围，保证切缘阴性，同时行常规淋巴结清扫，术后辅助放化疗改善预后；IG型ICC可行解剖性肝切除，需注意胆管切缘阴性和有无胆管癌栓。根据术前影像学检查及术中探查情况确定是否行淋巴结清扫以及什么部位的淋巴结清扫。对于近肝门部ICC考虑开展胃小弯淋巴结清扫，对于左肝外周型ICC选择性地开展胃底周围淋巴结清扫，但对于术前影像学检查提示有淋巴结转移但无特殊部位或远处转移的ICC，不建议扩大清扫范围[30]。基于ICC细胞起源及大体分型异质性而提出的不同手术方法，符合疾病个体化治疗的理念，结合癌症综合治疗思想，是实现ICC个体化、规范化治疗、改善ICC患者预后的一个可能的方向。

1.4　联合肝外胆管和血管切除

　　对术中病理证实胆管切缘阳性的较晚期患者，需在肝切除基础上联合肝外胆管切除。如左右肝管汇合部胆管侵犯范围较局限，可行受侵胆管汇合部切除，证实保留肝内胆管切缘及肝外胆管切缘阴性后，行胆管两切缘对端吻合[13]。既往通常将肝脏恶性肿瘤合并门静脉、下腔静脉等主要血管侵犯视为手术治疗的禁忌证，随着外科技术的发展，越来越多的学者认为合并肝静脉、门静脉、下腔静脉侵犯的肝脏恶性肿瘤可行手术切除、人造血管重建[31]。Miyata等[32]研究报道，合并肝中静脉切除与否的两组ICC根治患者，术后五年总体生存率和阴性切缘率之间差异无统计学意义。一项多中心大宗病例（1 087例）研究[33]报道指出，ICC根治术时联合主要血管切除，并不会增加患者术后并发症发生率，其术后整体生存率和无复发生存率与单纯解剖性肝切除组相比差异无统计学意义，认为在ICC手术治疗中实施下腔静脉切除、

门静脉切除或两者联合切除是安全可行的。

1.5 复发ICC外科治疗

文献[34-35]报道ICC术后复发率可高达55%~70%，肝脏是最常见的复发部位。Ohira等[34]发现再次行手术治疗的复发ICC患者中位生存期（36.7个月）显著高于未再行手术治疗者（13.1个月），并指出再次手术、肿块型肿瘤、无胆管侵犯是复发型ICC患者的有利预后因素，建议对局部复发的ICC患者行手术治疗。Si等[36]回顾性分析了72例ICC复发并再次获得R_0切除的患者资料，发现复发的ICC患者经再次手术后的1、2、3年术后生存率分别为82.9%、53.0%、35.3%，认为再次肝切除术对于部分复发ICC可获得较好的生存预后，而多复发灶、1年内复发、复发病灶直径>3 cm和肝硬化是影响再次手术预后的独立危险因素。Bartsch等[37]亦指出，与接受化疗、经动脉化疗栓塞、选择性内部放疗、射频消融或支持治疗的复发ICC患者相比，接受再次手术的患者有更长的总体生存时间（$P<0.001$）。

1.6 其他外科治疗

目前多认为ICC患者肝移植效果治疗效果差，有限的资料表明，移植术后肿瘤复发时间短、生存率低，甚至将ICC作为肝移植的禁忌证[38]。但Fu等[39]研究了11例ICC患者行肝移植术的术后生存资料，发现患者术后4年无复发生存率可达51.9%，整体生存率为50.5%，认为对于部分不可切除的ICC患者可经肝移植获得较好的预后。ICC局部治疗方法包括经动脉化疗栓塞术（TACE）、射频消融（RAF）、放射性钇栓塞等。Boehm等[40]通过Meta分析发现，在无法手术切除的ICC患者中，行肝动脉灌注（hepatic arterial infusion，HAI）、放射性钇栓塞、TACE和药物洗脱珠TACE的患者中位生存时间分别为22.8、13.9、12.4个月和12.3个月。

2 辅助治疗

2.1 辅助放化疗

ICC辅助性化疗的主要适应证为术后存在残余肿瘤或淋巴结转移患者[41]，可使用的化疗药物包括吉西他滨、铂类、卡培他滨或氟尿嘧啶类等抗肿瘤药。ICC的全身化疗一般参考晚期胰腺癌的方案，包括吉西他滨单药，吉西他滨与卡培他滨联合应用，以及吉西他滨与铂类似物(顺铂、奥沙利铂和卡铂)联合应用等。Valle等[42]针对晚期胆道

肿瘤的临床研究结果表明：吉西他滨和顺铂联合应用后的患者生存率优于吉西他滨单药。但ICC整体化疗效果欠佳，获益患者比例并不高，这与ICC高度异质性不无关系，而关于不同类型的ICC化疗反应性的研究也相对较少。研究[43]研究报道，以吉西他滨为基础的化疗可以提高管周浸润型、肿块型+管周浸润型患者（8% vs. 37%，$P<0.001$）和有淋巴结转移ICC患者的5年生存率。针对ICC术后辅助性放疗的研究同样较少。Jiang等[44]纳入了90例行手术治疗的ICC，放疗组（24例）的中位生存时间是19.1个月，无放疗组（66例）的中位生存时间是9.5个月，两者之间存在统计学差异（$P=0.011$）。Shroff等[45]进行的一项II期临床试验表明，与吉西他滨/顺铂治疗进展期胆管癌的历史对照相比，吉西他滨/顺铂联合白蛋白结合性紫杉醇（albumin-bound paclitaxel）治疗延长了患者总体生存时间和无病生存时间。

2.2 靶向治疗

随着二代测序等分子检测技术的完善，ICC突变基因和信号通路异质性得以逐渐揭示[1, 46]。随着精准医疗计划的提出和癌症基因组学的研究进展，靶向治疗有望实现真正意义上的根据ICC基因异质性进行的治疗。目前已有靶向IDH基因、FGFR通路EGFR受体、RAS/RAF/MEK/MAPK通路等大量的分子靶向治疗的临床试验。Saha等[47]通过对17种胆管癌在内的一大组癌细胞系的高通量药物筛选的研究发现，达沙替尼对于IDH突变的ICC效果显著，达沙替尼处理后的IDH突变异体种植瘤表现出明显的细胞凋亡和肿瘤消退。Loaiza-Bonilla等[48]报道了1例放化疗低反应性伴全身多发转移的IV期ICC患者，基于其BRAF V600E突变阳性的特点，将其作为dual-BRAF和MEK抑制剂治疗的候选者使用达帕菲尼联合曲美替尼治疗，结果展现出了良好的耐受性和反应性，达到了持续的症状和影像学改善，成为首个依据个体化基因组信息成功治疗ICC的案例。

2.3 免疫治疗

寻找ICC突变基因中的免疫原性表位是检查点抑制剂发挥作用的关键。Schumacher等[49]研究表明，20%的ICC存在IDH1（R132H）基因突变，含有适用于突变特异性疫苗接种的免疫原性表位，该突变区域的肽诱导CD4+免疫应答反应具有用于制备特异性IDH1（RI32H）基因疫苗的潜力。FDA于2017年批准PD-1抑制剂Pembrolizumab

（Keytruda）用于治疗携带一种特定基因特征（高度微卫星不稳定性，MSI-H或错配修复缺陷，dMMR）的任何实体瘤，包括胆道恶性肿瘤。成功治疗案例已见报道，Sui等[50]报道了2例IIIb期ICC（基因特点：dMMR阳性，MSS，肿瘤负荷为2.95~7.09个/Mb）患者，在化疗结合PD-1阻断后达到完全缓解。

2.4　新辅助治疗

ICC新辅助治疗临床应用较少，NCCN指南亦未无ICC患者术前行新辅助治疗疗相关问题的解释。Le Roy等[51]研究发现，39例进展期ICC在接受中位时间为6个周期的术前化疗后行手术治疗，其术后复发率、病死率和中位生存时间与112例单纯早期手术者相比差异无统计学意义（24.1个月vs. 25.7个月），认为新辅助化疗序贯手术治疗的局部晚期ICC患者的短期和长期预后与单纯早期手术切除的ICC患者相似，对局部进展期ICC具有降期作用，可增加手术机会。Kato等[52]报道1例局部进展期的ICC患者行新辅助放化疗，使用吉西他滨联合顺铂化疗、联合放疗后，成功进行左肝联合尾状叶切除。

2.5　结语

从ICC生物学异质性出发，结合个体化基因特点和大体分型，采取相应的手术方式和辅助治疗方案是改善ICC患者预后的新思路，尤其是在二代测序等生物技术飞速发展的今天，与患者分子生物病理学、基因表达特征相匹配的个体化诊断和综合治疗将成为可能，但仍需要更多的基础与临床研究对ICC患者进行分层或分子分型，区分化疗获益、靶向治疗获益或者免疫治疗获益的人群。

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