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述评 EDITORIAL

肝内胆管细胞癌术后复发转移机制与临床防治策略

盛 霞, 秦建民

盛霞, 复旦大学附属闵行医院病理科 上海市 201100

秦建民, 海军军医大学第三附属医院普外科 上海市 201805

秦建民, 教授, 主任医师, 研究方向为肝癌复发、转移机制与纳米靶向药物治疗.

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作者贡献分布: 本文由盛霞和秦建民完成; 秦建民修改润色.

通讯作者: 秦建民, 教授, 主任医师, 201805, 上海市嘉定区墨玉北路700号, 海军军医大学第三附属医院普外科. jianminqin@yahoo.com

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Mechanism of postoperative recurrence and metastasis of intrahepatic cholangiocellular carcinoma and clinical prevention and treatment strategy

Xia Sheng, Jian-Min Qin

Xia Sheng, Department of Pathology, Affiliated Minhang Hospital, Fudan University, Shanghai 201100, China

Jian-Min Qin, Department of General Surgery, The Third Hospital Affiliated to Naval Military Medical University, Shanghai 201805, China

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Corresponding author: Jian-Min Qin, Professor, Chief Physician, Department of General Surgery, The Third Hospital Affiliated to Naval Military Medical University, No. 700 North Moyu Road, Shanghai 201805, China. jianminqin68@hotmail.com

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Abstract

Intrahepatic cholangiocellular carcinoma is a primary adenocarcinoma originating from intrahepatic bile duct epithelial cells. The tumor has no capsule. At the early stage of the tumor, there are infiltration and metastasis along the lymphatic vessels, blood vessels, perineural space, and loose fibrous connective tissue, which are characterized by lymph node metastasis. Due to the absence of characteristic clinical manifestations and the lack of specific molecular markers for early diagnosis, the surgical resection rate is low and the postoperative tumor recurrence and metastasis rate is high. Low efficacy of chemoradiotherapy, molecular targeted drugs, and immunotherapy results in the poor prognosis. Further research of molecular pathology, gene function, and imaging technology can help elucidate the occurrence, recurrence, and metastasis mechanism of intrahepatic cholangiocellular carcinoma to improve its early diagnosis rate and precise clinical staging. Individualized precision treatment and prevention for the risk factors to reduce the recurrence and metastasis rate postoperatively are key to improving the patient prognosis.

Key Words: Intrahepatic cholangiocellular carcinoma; Recurrence and metastasis; Mechanism; Treatment; Prevention

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摘要

肝内胆管细胞癌是一种源于肝内胆管上皮细胞的原发性腺癌, 肿瘤无包膜, 肿瘤早期沿胆管周围淋巴管、血管、神经周围间隙及疏松纤维结缔组织等发

生多途径浸润转移, 以淋巴结转移为特征. 由于早期无特征性临床表现, 缺乏早期诊断特异分子标志物, 手术切除率低, 术后肿瘤复发转移率高, 放化疗、分子靶向药物和免疫治疗疗效低, 预后差. 通过分子病理学、基因功能、影像技术深入研究, 阐明肝内胆管细胞癌发生、复发转移机制, 提高早期诊断率和精准临床分期, 针对肿瘤复发转移危险因素采用个体化的精准治疗方案和预防措施, 是降低肝内胆管细胞癌术后肿瘤复发与转移率, 改善患者预后的关键.

关键词: 肝内胆管细胞癌; 复发转移; 机制; 治疗; 预防

核心提要: 肝内胆管细胞癌手术切除率低, 术后肿瘤复发转移率高, 放化疗、分子靶向药物和免疫治疗疗效差, 阐明肝内胆管细胞癌发生、复发转移机制, 针对肿瘤复发转移危险因素采用个体化的精准治疗方案和预防措施, 才能降低肝内胆管细胞癌术后肿瘤复发与转移率, 改善患者的预后.

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0 引言

肝内胆管细胞癌(intrahepatic cholangiocellular carcinoma, ICC)是一种源于肝内胆管上皮细胞的原发性腺癌, 占肝脏原发恶性肿瘤的5%-20%, 发病率仅次于肝细胞癌, 位居第2位, 与肝内胆管结石、原发性硬化性胆管炎、寄生虫感染、病毒性肝炎等因素密切相关, 其中与肝胆管结石的关系最为密切. ICC肿瘤无包膜, 肿瘤早期沿胆管周围淋巴管、血管、神经周围间隙及疏松纤维结缔组织等发生多途径浸润转移, 以淋巴结转移为特征, 肿瘤侵袭、转移的恶性程度高于肝细胞癌[1,2]. ICC术后61.1%出现复发, 其中64.6%患者术后12 mo内复发, 21.7%患者术后12 mo-24 mo复发, 8.4%患者术后24 mo-36 mo复发, 5.3%患者术后36 mo复发[3]. 即使获得R0切除, ICC术后5年复发率仍高达53.5%-73.4%, 在术后复发ICC患者中, 23.9%为手术切缘复发, 29.3%为肝内复发, 14.8%为肝外复发, 32%为肝内和肝外同时复发; 肝外复发部位主要包括肺、淋巴结、腹膜、骨和肾上腺, 手术切缘复发和肝内复发多见于术后6 mo内, 肝外复发于术后2年内发生[4-6]. 早期和晚期ICC肿瘤复发的临界值为24 mo, Zhang等[5]分析发现ICC术后早期复发为78.8%, 晚期复发为21.2%, 早期肝外复发高于肝内复发(44.1% *vs* 28.3%), 晚期肝内复发高于肝外复发(55.9% *vs* 71.7%). ICC患者术后1、3、5年肿瘤复发率分别为60.4%、79.6%、89.3%, 血清HBsAg阳性患者术后1、3、5年肿瘤复发率分别为36.7%、56%、75.0%, 肿瘤大于5 cm患者术后1、3、5年肿瘤复发率分别为73.8%、87.5%、94.3%, Child-Pugh评分B级患者术后1年内肿瘤复发率为83.3%, 淋巴结转移患者术后1、3、5年肿瘤复发率分别为81.3%、97.8%、100%[7].

ICC淋巴结转移、血管、神经周围、胆管侵犯发生率分别为34%、38%、29%、29%, 年龄较大、肿瘤较大、多中心肿瘤及卫星病灶、淋巴结转移、血管及神经周围侵犯、手术切缘阳性、大范围肝切除、肝外胆管切除、肝硬化、慢性乙肝、多次输血、肿瘤分化差与ICC术后肿瘤复发转移发生率高密切相关[8]. ICC肝移植术后复发率为54.5%, 根治性切除术后5 年生存率为20%-40%, 局部消融治疗5年生存率为24%, ICC对放化疗、分子靶向药物和免疫治疗疗效低, 总有效率为19%-36%[9-11]. ICC手术切缘组织学阳性和淋巴结转移与术后肿瘤复发密切相关, 复发后患者中位生存期为11.1 mo, 复发后再次接受肿瘤切除的患者中位生存期为26.7 mo[10]. 由于ICC早期无特征性临床表现, 缺乏早期诊断特异分子标志物, 就诊时多为中晚期, 手术切除率低, 即使手术切除, 术后肿瘤复发转移率高, 放化疗、分子靶向药物和免疫治疗疗效低, 患者预后差. 如何提高ICC早期诊断率和R0切除率, 降低术后肿瘤复发与转移, 是目前ICC亟待解决的关键问题, 本文结合相关文献, 探讨ICC术后肿瘤复发转移危险因素、机制与临床防治策略.

1 肿瘤复发转移相关危险因素

与肿瘤<5 cm相比, 肿瘤≥5 cm ICC术后复发中位时间更短(5 mo *vs* 11 mo), 有微血管癌栓者术后复发中位时间短于无癌栓者(6 mo *vs* 54 mo), 有淋巴结转移者术后复发中位时间短于无转移者(5 mo *vs* 8 mo), 糖类抗原19-9(carbohydrate antigen 19-9, CA19-9)≥100 U/mL术后复发中位时间短于<100 U/mL(9 mo *vs* 27 mo), 肿瘤≥5 cm、微血管癌栓、淋巴结转移、CA19-9≥100 U/mL是影响ICC术后肿瘤复发的独立危险因素(P<0.05)[12]. 手术切缘阳性的ICC患者术后复发率为60.29%, 远处转移率为42.65%, 显著高于切缘阴性术后复发率为22.06%, 远处转移率为27.94%[13]. 有淋巴结转移(N1)的ICC患者术后肿瘤中位复发时间短于无淋巴结转移(N0)的患者(7 mo *vs* 22 mo)[14]. 等待肝移植时间>100 d的ICC患者肝移植术后肿瘤复发率是等待时间<100 d患者的4倍[15]. 周围神经侵犯的ICC患者83%术后发生肿瘤复发[16]. 多发性肿瘤、淋巴结转移、微血管侵犯(microvascular invasion,

MVI)、谷丙转氨酶(alanine transaminase, ALT)升高、谷氨酰转肽酶(glutamyltransferase, GGT)升高、甲胎蛋白(alpha-fetoprotein, AFP)升高、谷氨酰转移酶与血小板比值(glutamyltransferase to platelet ratio, GPR)升高、白蛋白与碱性磷酸酶比值(albumin to alkaline phosphatase ratio, AAPR)下降、白蛋白与谷氨酰转移酶比值(albumin to glutamyltransferase ratio, AGR)下降、肿瘤淋巴结转移(tumor node metastasis, TNM)分期晚期是ICC术后肿瘤复发的危险因素[17]. 与MVI(-)的宽切缘(≥1 cm) ICC患者相比, MVI(+)的宽切缘术后ICC患者肿瘤复发风险增加约1.5倍, 切缘和MVI是影响HBV相关ICC患者术后肿瘤复发的独立危险因素[18]. CA19-9升高、多发肿瘤、微血管侵袭、大血管侵犯、淋巴结转移和R1切除与ICC术后早期复发密切相关[19,20]. 肿瘤内血管包裹肿瘤簇的存在和PD-L1表达升高具有侵袭性肿瘤特征, 肿瘤内血管包裹肿瘤簇和低淋巴细胞-单核细胞比率(lymphocyte-monocyte ratio, LMR)与ICC术后早期肿瘤复发显著相关[21,22]. 大血管侵犯、微血管侵犯比无血管侵犯的ICC患者更容易发生肝外复发(P<0.05)[23]. 肝内胆管结石合并ICC患者比不合并肝内胆管结石的ICC患者发生周围神经侵犯与脉管癌栓的概率高, 术后易发生肿瘤复发转移[24].

不同的炎性反应细胞抗肿瘤和促肿瘤作用不同, 中性粒细胞与淋巴细胞比值(neutrophil lymphocyte ratio, NLR)能够反映免疫平衡状态, NLR升高提示中性粒细胞相对升高和淋巴细胞相对降低, 高NLR表明患者免疫状态失衡而处于促肿瘤状态[25,26]. NLR≥2.3的ICC患者, 血CEA水平、多发肿瘤和淋巴转移和血管侵犯比例高、肿瘤直径较大, NLR≥2.3患者术后1、3、5年肿瘤复发率显著高于NLR<2.3患者(49%、70%、80% *vs* 35%、57%、65%, P<0.01); CEA>10 μg/L、CA19-9>39 u/L、NLR≥2.3、肿瘤直径≥5 cm、肿瘤多发、淋巴结转移、血管侵犯是ICC术后肿瘤复发的独立危险因素, NLR≥2.3的患者术后肿瘤复发率更高[27]. 与低微淋巴管密度(microlymphatic vessel density, MLVD)相比, 高MLVD的ICC患者淋巴结转移更高, 低MLVD更容易发生肿瘤复发, 肿瘤相关淋巴管生成与ICC患者淋巴转移增加、肿瘤复发显著相关(P<0.001), 术中淋巴结活检评估肿瘤相关淋巴管生成, 不仅指导选择淋巴结切除, 而且为术后治疗方案提供指导[28]. HBV感染ICC患者术后1、3、5年肿瘤复发率分别为44.6%、65.4%、73.8%, 非HBV感染患者分别为41.9%、66.2%、78.2%, HBV感染患者中, NLR低患者术后1、3、5年肿瘤复发率显著低于NLR高的患者(34.6%、55.9%、62.7% *vs* 51.2%、71.4%、80.2%, P<0.001). NLR低无HBV感染ICC患者术后1、3、5年肿瘤复发率与NLR高无HBV感染患者无显著性差异(35.9%、61.5%、73.3% *vs* 44.6%、68.6%、81.0%, P>0.05), 表明NLR升高是乙肝病毒相关ICC患者术后肿瘤复发的独立危险因素[29]. ICC肿瘤周围浆细胞样树突状细胞(plasmacytoid dendritic cells, pDCs)浸润提示肿瘤周围存在免疫耐受微环境, pDCs高的ICC患者术后1、3、5年累计复发率高于pDCs低的患者(41.0%、64.7%、69.5% *vs* 29.0%、38.4%、48.2%, P<0.05)[30]. 由于涉及ICC术后肿瘤复发转移因素较多, 针对上述诸多因素进行分析, 采取个体化的防治措施, 对降低ICC术后肿瘤复发转移具有十分重要意义.

2 肿瘤复发转移机制

ICC肿瘤组织中CD90、DKK1、PRR11、MMP9、TGF-β1、EpCAM蛋白高表达, 导致胆管癌细胞增殖、侵袭能力增强, 极易侵犯血管、淋巴管, 导致术后肿瘤复发转移[31-35]. ICC肿瘤组织中E-cadherin表达明显低于癌旁组织(42% *vs* 68%), Vimentin表达明显高于癌旁组织(50% *vs* 30%)(P<0.05), 肿瘤组织E-cadherin表达下降和Vimentin表达上升促进胆管癌细胞侵袭、转移, 导致血管癌栓、淋巴结和肿瘤转移[36]. Fascin蛋白是一种细胞骨架蛋白, 在ICC肿瘤组织中高表达(55.2%), 而正常肝内胆管组织中不表达, 中低分化癌组织表达显著高于高分化癌组织(74.3% *vs* 26.1%, P<0.05), Fascin-1与F-actin蛋白结合改变细胞膜结构, 增加癌细胞迁移、转移能力, 参与肿瘤侵袭及转移[37]. 转移抑制因子(metastasis suppressor 1, MTSS1)是一种细胞骨架支架蛋白, 调节肌动蛋白的相互作用, 促进细胞间连接, MTSS1表达缺失促进胆管癌细胞迁移, 导致肿瘤复发转移[38]. 硒结合蛋白1(selenium-binding protein 1, SBP1)在ICC肿瘤组织中表达明显下调, SBP1表达降低与微血管侵犯、淋巴转移、TNM分期密切相关, SBP1低表达导致波形蛋白(vimentin)和蜗牛蛋白(snail)等间充质标志物上调, E-cadherin下调, 增强胆管癌细胞上皮间质转化(epithelial mesenchymal transformation, EMT)过程, SBP1减少可能通过激活EMT过程增强癌细胞迁移和侵袭, 促进肿瘤转移[39]. 52.6%阴性粘蛋白ICC患者肿瘤细胞表达CD133, $CD133^+$患者肿瘤细胞TGF-β1/p-Smad2表达升高及EMT样改变(E-Cadherin表达缺失, Vimentin、S100A4表达升高), 促进肿瘤复发转移[40]. 三方基序蛋白44(tripartite motif-containing protein 44, TRIM44)通过下调E-cadherin表达, 上调vimentin、β-catenin和Snail表达, 诱导胆管癌细胞EMT和凋亡抵抗, 促进ICC肿瘤复发转移[41]. 神经纤毛蛋白1(neuropilin-1, NRP1)在ICC肿瘤组织高表达, 激活p-FAK/p-PI3K/p-AKT信号通路, 促进胆管癌细胞增殖和迁移[42]. 骨桥蛋白(osteopontin, OPN)在ICC肿瘤组

织低表达, OPN通过负调控ICC细胞MMP1、MMP10、CXCR4表达增强ICC细胞增殖、迁移和侵袭能力, 循环OPN/体积低水平提示ICC患者肿瘤侵袭性强, 术后易复发[43]. 肿瘤坏死因子受体相关因子4(tumor necrosis factor receptor-associated factor 4, TRAF4)通过激活AKT信号通路促进胆管癌细胞迁移和侵袭, 导致ICC术后累积复发率增加[44]. S100A11调控细胞周期、分化, 通过SMAD2/3信号通路促进胆管癌细胞TGF-β1诱导的EMT, 导致ICC肿瘤转移[45]. 泛素样PHD和无名指结构域2(ubiquitin-like with PHD and ring finger domains 2, UHRF2)抑制胆管癌细胞E-cadherin表达, 参与ICC微血管侵犯及淋巴转移[46]. ICC肿瘤组织中B7-H4上调胆管癌细胞Vimentin和snail表达, 下调E-cadherin表达, 导致EMT, 诱导胆管癌细胞高表达Bcl-2和低表达Bax和裂解的caspase-3, 抑制癌细胞凋亡、激活ERK1/2信号等途径促进胆管癌细胞增殖、侵袭和迁移[47]. 肿瘤组织VEGFR-3阳性表达促进术后肿瘤相关淋巴管生成、淋巴结转移, VEGFR-3阳性表达与肿瘤淋巴结转移及肿瘤复发显著相关[48]. 早期复发的ICC患者CTLA-4的表达密度高于未早期复发ICC患者, CTLA-4在TILs中过表达促进ICC的侵袭转移[49].

ICC常见基因突变包括成纤维生长因子受体(fibroblast growth factor receptor, FGFR)1-3融合/突变和扩增(11%-17%)、异柠檬酸脱氢酶(isocitrate dehydrogenase, IDH)IDH1/2突变(5%-36%)、MCL1放大(21%)、BAP1变异(13%)、RNF43突变(9%)、PIK3CA突变(3%-9%)、BRAF突变(3%-7%)、HER2扩增/突变(7%)、MET扩增(2%-7%)、MET突变(5%)、ARID1A突变(6.9%-36%)、CDKN2A/B缺失(5.6%-25.9%)、KRAS突变(8.6%-24.2%)、SMAD4突变(3.9%-16.7%)、MLL3突变(14.8%)、PTEN基因突变(0.6%-11%)、ARAF变异(11%)、ROBO2变异(9.3%)、ERBB3扩增(7%)、NRAS突变(1.5%-7%)、CDK6突变(7%)、PEG3突变(5.6%)、XIRP突变(5.6%)、RB1突变(5%)、BRCA1/2突变(4%)、NF1突变(4%)、TSC1突变(4%)、RADIL突变(3.7%)、NDC80突变(3.7%)、PCDHA13突变(3.7%)、LAMA2突变(3.7%)、EGFR突变(1.5%-2%)、CTNNB1突变(0.6%), 这些基因的异常扩增或突变导致DNA修饰、表观遗传和信号转导通路发生异常, 使胆管癌细胞增殖异常、侵袭迁移能力增强[50]. IDH突变导致2-羟戊二酸(2-hydroxyglutarate, 2-HG)水平上调, 促使肝细胞核因子4α(hepatocyte nuclear factor 4α, HNF4α)活性增强, DNA及组蛋白处于高甲基化状态, 引起基因组高甲基化修饰的表观遗传改变和细胞的异常分化, 而且IDH1突变诱发胆管炎性反应, 促进THP-1巨噬细胞系从M1向M2型极化, 分泌白细胞介素(interleukin, IL)-10、IL-12和转化生长因子-β(transforming growth factor beta, TGF-β)等细胞因子, 导致ICC发生发展[51-53]. Wang等[54]研究发现IDH1/2突变的ICC患者术后1、4、7年肿瘤复发率显著低于IDH野生型ICC患者(10.5%、45.3%、45.3% *vs* 41.7%、71.5%、81.3%). 29.5%复发ICC肿瘤发生SLIT2突变, SLIT2失活突变导致ICC细胞中PI3K-Akt信号通路激活, 直接增强中性粒细胞趋化性, 介导肿瘤相关中性粒细胞浸润, 促进胆管癌细胞侵袭转移[55]. Lnc-LFAR1能够降低胆管癌细胞E-cadherin水平, 增强vimentin表达, 上调TGF-β1和Smad2、Smad4表达, 促进胆管肿瘤复发与转移[56]. ICC肿瘤细胞上述蛋白分子表达异常、基因扩增/突变引起细胞周期、凋亡或信号转导通路异常使胆管癌细胞异常增殖、侵袭和迁移能力增强, 导致ICC术后肿瘤复发或转移, 利用分子生物学技术阐明参与胆管癌细胞增殖、侵袭和迁移密切相关分子和基因的确切机制, 是防治ICC发生、发展的关键.

3 治疗

ICC肿瘤复发转移中, 44.8%肿瘤切除部位复发、24.1%淋巴结转移、31%肿瘤切除部位复发和淋巴结转移, 最常见的淋巴结转移部位是腹主动脉周围淋巴结, 其次是腹腔动脉、肝总动脉和肝十二指肠韧带淋巴结, 高比例的复发仅发生在潜在的放疗位势区范围内[57]. ICC肿瘤复发或转移治疗方法取决于肿瘤复发或转移部位、数目、肝功能及全身状况, 再次手术切除仍然是治疗ICC肿瘤复发或转移最有效的治疗方法, 但仅少数患者有机会接受根治性手术治疗, 肿瘤局部治疗、放化疗、分子靶向药物和免疫治疗是复发或转移性ICC更为重要的治疗措施.

3.1 手术 对于初次接受R0切除、肝内单发复发病灶、无淋巴结转移、复发时间>2年的复发性ICC, 再次手术切除率为9.7%-28.5%[10,58]. Yamashita等[59]研究发现17%术后复发ICC患者接受再次手术治疗, 术后2、5年生存率分别为87%、44%, 与首次手术治疗原发性ICC生存率相似, ICC复发再切除的远期预后优于其它治疗(5年生存率, 48% *vs* 44%). 复发性ICC患者可从反复手术切除中获益, 与重复可切除性相关的因素是首次切除时的CA19-9、手术切除状态(R0/R1/Rx)及中位复发时间[60]. ICC复发再手术适应证[58,61,62]: (1)单发肿瘤或多发肿瘤数量2-3个, 最大肿瘤直径<5 cm; (2)靛青绿留滞试验中15 min后滞留≤20%; (3)全身情况良好, 肝功能Child-Pugh分级为A/B级; (4)无肝内外同时存在多个转移病灶; (5)初次手术时无明显肝内血管癌栓; (6)无可能导致严重并发症的基础疾病. 再次手术前需要严格进行术前评估确保剩余肝脏有足够的肝脏储备功能, 术式依据肿瘤大小、位置

和残肝体积进行选择, 若残肝体积足够且复发肿瘤为单发, 靛青绿留滞试验中15 min后滞留≤20%, 剩余肝体积≥40%, 可选择规则性肝段或肝叶切除术; 若复发性肿瘤直径>5 cm, 或靠近大血管、位于肝门部等特殊位置, 宜选择肿瘤局部切除[63,64]. 复发ICC患者接受二次切除手术后的中位生存时间明显高于肝动脉化疗栓塞患者(26.1 mo *vs* 9.6 mo)[10]. 复发ICC经再次手术治疗术后1、2、3年生存率分别为82.9%、53%、35.3%,术后1、2、3年复发率分别为53.2%、80.2%、92.6%, 表明肿瘤再次切除使复发ICC患者可获得较好的生存预后, 但仍存在较高肿瘤复发率, 肝硬化、肿瘤多发、肿瘤直径>3 cm、复发时间<12 mo是影响复发肿瘤再切除的不良预后因素[65]. 与肝动脉栓塞化疗、全身化疗相比, ICC复发肿瘤再切除可显著延长患者中位生存(26.1 mo *vs* 9.6 mo、16.8 mo), 对于孤立的复发灶, 再手术切除率为9%-30%, 但50%以上再切除患者术后11.5 mo内再次复发[10,58]. ICC肿瘤复发患者再次手术是否需要淋巴结切除和预防性化疗, Asaoka等[66]研究发现ICC淋巴转移率为54.4%, 其中肝十二指肠淋巴转移率为54.8%, 肝总动脉旁淋巴结为35.4%; 有淋巴结转移的ICC患者术后复发率为32%, 术中淋巴结清扫只对CA19-9水平正常的ICC患者有效, 对于没有淋巴结转移ICC患者, 不常规行预防性淋巴结清扫; 有淋巴结转移的ICC患者术后辅助化疗显著获益, 对肿瘤直径>5 cm且有肝内转移或淋巴结转移的患者术后应进行辅助化疗; 有淋巴结转移ICC患者接受辅助化疗、不接受辅助化疗的患者5年总生存期(overall survival, OS)率分别为61.2%、18.3%, 辅助化疗显著延长患者OS, 但对于CA19-9升高的ICC患者,辅助化疗无明显获益. 淋巴结清扫没有显著提高淋巴结阴性ICC患者的生存率, 淋巴结切除范围对HBV相关ICC患者的生存无显著影响, 常规淋巴结清扫不推荐, 如果术中淋巴结检查提示淋巴结转移阳性时, 应进行淋巴结切除[67]. 严格掌握再次手术指征, 术中淋巴结清扫、术后辅助治疗需要依据淋巴结转移情况、是否存在肿瘤复发转移的高危因素.

3.2 *肝移植* 由于肝源短缺, 目前肝移植主要用于良性终末期肝病的治疗, 而对于ICC而言, 单发肿瘤、直径≤2 cm的极早期ICC患者肝移植术后5 年生存率为65%, 局部进展期ICC(单发肿瘤直径>2 cm, 或局限于肝脏多发肿瘤, 无肝外、大血管或淋巴结转移)肝移植术后5 年生存率为45%, 建议对单发肿瘤直径≤2 cm, 无法手术切除的ICC行肝移植治疗[68,69]. Facciuto等[70]研究发现符合米兰标准的ICC肝移植术后肿瘤复发率为10%, 5年生存率为78%. 而对于手术切除后肿瘤复发的ICC患者, 如果复发肿瘤为单发、复发时间超过6 mo, 行肝移植术后可获长期生存(185 mo)[57]. 对于术前未接受抗肿瘤化疗的ICC患者, 接受肝移植治疗术后3年生存率为50%-65%[71,72]. Hong等[73]研究发现对于局部进展期ICC(肝实质浸润、多发肿瘤、肿瘤直径≥5 cm、病理分化不良、淋巴血管侵袭、局部淋巴结转移、神经侵袭等)患者, 术前接受新辅助治疗联合术后辅助治疗、术后辅助治疗、术后无辅助治疗接受肝移植术后5年生存率分别为47%、33%和20%(P<0.05). ICC潜在的肝移植选择标准: (1)极早期肿瘤(单个肿瘤, 肿瘤大小≤2 cm)伴肝硬化; (2)局部进展期肿瘤联合新辅助化疗. 依据此标准选择肝硬化和极早期ICC(单个肿瘤≤2 cm)患者肝移植1年、3年、5年OS分别为93%、84%、65%, 局部进展期肿瘤联合新辅助化疗的ICC患者肝移植术后1年、3年和5年OS分别为100%、83.3%、83.3%[74]. 早期ICC患者(包括单发、高分化、直径≤2 cm)肝移植术后1年、3年、5年生存率分别为93%、84%、65%, 高于晚期ICC患者(多发、中低分化、直径>2 cm)61%、47%、30%[75]. 因此借鉴早期和局部进展期ICC肝移植治疗经验, 对于术后复发的ICC肝移植前新辅助治疗联合术后辅助治疗是提高患者肝移植术后生存期非常重要措施, 而且应严格掌握肝移植治疗指征, 对于不适合再次手术切除且符合上述肝移植标准的复发ICC患者, 可以选择合适的患者行肝移植. 由于术后复发的ICC肝移植治疗临床研究较少, 关于术后复发ICC行肝移植治疗指征、时机、免疫抑制剂应用、辅助治疗等问题需要国内外多中心、前瞻性的研究.

3.3 *化疗* ICC复发患者全身化疗中位生存期为16.8 mo[10]. Sui等[76]报告2例ICC术后复发患者采用派姆单抗联合替加氟化疗, 其中1例化疗3个周期后使用了15个周期派姆单抗, 另一例化疗5个周期后使用了6个周期派姆单抗, 复查CT和磁共振显示病灶均明显缩小, 腹腔内肿大的转移淋巴结均消失, 疾病无进展生存期分别为16 mo和13 mo, 治疗期间均未出现派姆单抗相关不良反应. Kitano等[77]采用吉西他滨联合顺铂治疗复发性ICC患者中位生存期为16.8 mo. IDH突变的ICC患者首选吉西他滨联合顺铂化疗方案, 中位OS和中位无进展生存期(median progression-free survival, mPFS) 分别为11.7 mo和8 mo[78]. 肝内转移、肿瘤≥4.4 cm的ICC患者术后辅助化疗能够降低术后复发率, 提高患者生存期[59]. ICC术后复发行射频消融联合吉西他滨、顺铂方案治疗客观缓解率为79.2%, 术后1 mo肿瘤完全消融率为86.7%, 中位生存时间为28. 6 mo, 1、2、3年生存率分别为87.3%、69.3%、32.6%[79]. 对于具有复发或转移高危的ICC患者, 辅助化疗能够显著降低肿瘤复发或转移, 已有复发或转移的ICC, 但单一化疗疗效低, 化疗联合手术或局部治疗具有协同增效作用, 显著提高复发或转移ICC治疗效果.

3.4 局部消融治疗 消融治疗ICC局部肿瘤控制率和患者远期生存率差于肝细胞癌, 主要与ICC多无完整包膜, 容易侵犯邻近组织有关,导致肿瘤消融不全复发率高, 因此消融治疗需同时毁损肿瘤及癌旁0.5 cm-1 cm范围内肝脏组织, 才能达到足够消融区域[10]. ICC术后复发肿瘤直径中位数为1.5 cm(0.7 cm-4.4cm), 经射频消融治疗后mPFS为39.8 mo, 肿瘤<1.5 cm患者PFS显著高于≥1.5 cm者[80]. 复发性ICC患者接受二次手术及热消融治疗后中位生存期无显著性差异(26.1 mo *vs* 25.5 mo), 显著高于化疗(9.1 mo)[10]. 微波消融结合肝动脉栓塞化疗治疗ICC患者肿瘤完全消融率为92.3%, 中位无进展生存期(progression-free survival, PFS)和OS分别为6.2 mo和19.5 mo[81]. ICC术后复发经微波消融治疗后95%完全消融, 无瘤生存期1.5 mo-34.2 mo(中位5.6 mo); 6 mo、1年、2年、3年OS分别为94.6%、67.6%、40.5%、27.0%; 复发肿瘤直径是影响肿瘤局部消融术后累积生存率的主要危险因素和预后的唯一独立因素, 复发肿瘤直径>3 cm和术后早期复发(≤1年)是影响肿瘤局部消融术后无瘤生存期的独立危险因素, 对术后晚期复发、直径≤3 cm的肿瘤疗效更好[82]. 与外科切除相比, ICC术后复发肿瘤经微波消融治疗后5年OS(23.7% *vs* 21.8%)和3年RFS(33.1% *vs* 30.6%)相似, 但外科切除术后并发症高于微波消融(13.8% *vs* 5.3%, *P*<0.001); ICC术后局部肿瘤复发患者微波消融治疗后中位OS为12.1 mo (5.9 mo-29.8 mo), 1、3、5年OS分别为50%、21.5%、6.1%, 中位RFS为8.2 mo (2 mo-27 mo), 1、3、5年分别为41.1%、21.5%、6.1%, 肿瘤分化不良、乙型肝炎病毒感染、胆石症和淋巴结转移是影响微波消融术后预后的危险因素[83]. Xu等[84]研究发现复发ICC患者经微波消融术后中位OS为31.3 mo, 1、3、5年OS率分别为81.2%、42.5%、23.7%, 1、3、5年RFS率分别为70.3%、33.1%、0%, 再手术切除术后中位OS为29.4 mo, 1、3、5年OS别为77.4%、36.4%、21.8%, RFS分别为76.7%、30.6%、0%, 二者中位OS、OS、RFS无显著性差异(*P*>0.05), 肿瘤数量、转移和ALBI分级是影响OS危险因素, 微波消融可作为复发ICC安全有效治疗方法, 尤其肝功能为ALBI 2级的复发ICC患者, 可以作为首选治疗方法. 对于复发肿瘤>3 cm者, 再切除术后中位OS高于热消融治疗(20.5 mo *vs* 13.5 mo, *P*<0.05), 但术后1、2、3年OS与热消融无显著性差异(83.8%、38%、17.1% *vs* 69.8%、37.3%、20.5%, *P*>0.05)[85]. 对于复发ICC, 应选择肿瘤≤3 cm进行局部消融治疗, 而直径>3 cm, 尤其超过5 cm复发性ICC, 一次消融通常难于达到足够的消融区域致肿瘤消融不全, 导致肿瘤播散或多发转移, 应慎重选择消融治疗, 如果不能手术而选择局部治疗时, 消融联合TACE、放化疗等, 不仅提高消融疗效, 而且减少肿瘤残留和再复发转移.

3.5 肝动脉灌注或栓塞化疗 72%-100%ICC患者血管造影显示肿瘤部分或全部区域为高血供, 肿瘤表达血管内皮生长因子, 为肝动脉栓塞化疗(transarterial chemoembolization, TACE)提供了理论基础[85]. TACE治疗ICC适应证: 适用于肿瘤局限在某一肝段或肝叶, 肝功能Child A级, 肿瘤<8 cm高血供ICC, 但对于肿瘤多发并伴卫星灶, 缺乏血供及肝功能Child B级的复发性ICC患者, TACE不能显著延长患者生存期[86,87]. Liu等[88]研究发现ICC行R0切除术后辅助TACE治疗不能改善TNM Ⅰ期患者生存, TNM Ⅰ期ICC患者术后TACE治疗的肿瘤复发率高于非TACE(*P*<0.05), 术后辅助TACE是无复发生存期(recurrence free survival, RFS)恶化的独立预测因子, 根治性术后辅助TACE不能延缓肿瘤复发和延长TNM Ⅰ期ICC患者OS, 辅助TACE可能会增加TNM Ⅰ期ICC患者的复发风险, 不适合TNM Ⅰ期ICC患者. TACE治疗ICC术后局部复发患者中位OS为26.9 mo(8.3 mo-44.4 mo), 1、3、5年OS分别为69.6%、40.5%、21.7%, 中位RFS为26.9 mo(4.3 mo-44.4 mo), 1、3、5年RFS分别为62%、39.3%、21.7%, 肿瘤>5 cm、分化不良和大范围肝切除是影响TACE治疗疗效的独立预后因素[83].

肝动脉灌注化疗(hepatic artery infusion chemotherapy, HAIC) 是将顺铂、5-FU等化疗药物直接注入患者肿瘤局部供血动脉中, 减少血浆蛋白结合抗癌药物, 使肿瘤病灶局部的药物浓度升高, 有效杀灭肿瘤细胞, 发挥显著的抗肿瘤治疗效果, HAIC治疗使肿瘤部位药物浓度相当于全身经静脉化疗的10-30倍, 显著提高杀灭肿瘤细胞疗效, 抑制新生血管形成, 促进肿瘤消退[89]. 陈朝等[90]应用HAIC联合吉西他滨治疗进展期ICC, 有效率显著高于静脉化疗(83.3% *vs* 50%), 显著提高抗肿瘤效果. TACE或HAIC治疗能够显著提高ICC肿瘤组织局部药物浓度和杀灭肿瘤细胞作用, 降低化疗药物毒副作用, 尤其适用于肿瘤多发无法手术切除的复发ICC, 但由于ICC肿瘤多为少血供肿瘤, 影响TACE或HAIC疗效, 需要联合放疗、分子靶向药物或免疫治疗, 以提高TACE或HAIC疗效.

3.6 放疗 ICC肿瘤具有少血供、纤维化、无包膜、低分化高度恶性等特点, 利用高能量、穿透力强的射线(X线、电子线、γ射线等), 通过计算机模拟肿瘤适形, 能精准地保证肿瘤的照射剂量, 降低对正常组织的损伤, 破坏肿瘤细胞核中的DNA, 使细胞失去增殖能力, 从而杀死肿瘤细胞、控制肿瘤细胞生长[91]. 利用立体定向放射治疗(stereotactic body radiotherapy, SBRT)治疗无法手术的初发和复发ICC, 术后1、2年OS分别为45%、20%[92]. ICC术后复发接受^{90}Y治疗后患者3、5年OS优于未接受

放疗者(78%、40% *vs* 8%、8%, *P*<0.05)[93]. Kamphues等[94]经导管肿瘤局部注入^{192}铱治疗复发ICC, 1、5年生存率分别为77.1%和51.4%, 远期预后与手术再切除相似. SBRT治疗复发ICC中位OS为13.6 mo, 1年局部控制率为78.6%[95], Smart等[96]应用质子放射治疗复发ICC患者, 中位OS为25 mo, 2年局部控制率为84%. 放射治疗仍然是复发性ICC有效局部治疗方法, 肿瘤≥5 cm是复发患者中唯一与超过放疗区域复发相关因素, 17.2%患者在放疗区复发, 尤其对于肿瘤≥5 cm患者, 应谨慎选择辅助放疗[97]. 对于肿瘤较大、乏血供、侵犯大血管无法手术切除的复发或转移ICC, 放疗具有较好控制肿瘤生长作用, 联合化疗、分子靶向药物或免疫治疗, 是非手术治疗的重要措施.

3.7 *分子靶向药物治疗* 分子靶向药物是针对胆管细胞癌发生分子靶点(靶点基因、受体、抗原)的药物在分子水平治疗干预, 靶向药物通过体液途径到达肿瘤靶点区域, 特异性结合相应的致癌位点, 诱导肿瘤细胞凋亡、坏死或被机体免疫细胞所吞噬, 同时对肿瘤周围正常组织无损害的一种治疗药物. 分子靶向药物治疗的基础是肿瘤分子存在异质性改变, 这些分子的异质性被选择性地定位, 如培米替尼(pemigatinib)是一种高度选择性FGFR 1-3小分子抑制剂, 首个被美国FDA批准用于治疗晚期或转移性胆管癌的分子靶向药物, 与FGFR2野生型ICC患者相比, 培米替尼治疗FGFR2融合/重排患者疗效显著提高(CR, 3% *vs* 0%; PR, 33% *vs* 0%; SD, 47% *vs* 40%; PD, 15% *vs* 35%), 治疗FGFR2基因融合/重排ICC患者, 客观缓解率(objective response rate, ORR)为35.5%, PR为32.7%, 疾病控制率(disease control rate, DCR)为82%, 中位缓解持续时间(duration of response, DOR)为7.5 mo, 中位PFS和OS分别为6.9 mo和21.1 mo, 表明FGFR融合/重排患者是对分子靶向药物治疗最敏感的类型, 但由于胆管癌中FGFR 2 重排或融合突变的比例仅为6.14%, 限制了其临床应用[98]. 针对FGFR2分子靶向药物英菲格拉替尼(infigratinib)治疗ICC的DCR高达83.3%[99]. BRAF-V600E在ICC中突变率为3.3%, BRAF抑制剂达拉非尼治疗ICC患者ORR为41%, 54%患者缓解持续时间>6 mo, 中位PFS和OS分别为7.2 mo和11.3 mo[100,101]. 安罗替尼主要通过抑制VEGF/PI3K/AKT信号通路, 从而抑制肿瘤细胞增殖和侵袭, 促进肿瘤细胞凋亡, 由ICC患者来源的异种移植肿瘤模型(patient-derived tumor xenograft, PDX)显示安洛替尼治疗显著地抑制体内肿瘤的生长(抑瘤率为95.2%), 表明安罗替尼具有抗ICC肿瘤作用, 可以作为治疗ICC分子靶向药物[102]. 艾伏尼布(ivosidenib)治疗IDH1突变的胆管癌患者, DCR为53%, 中位PFS为3.8 mo(3.6 mo-7.3 mo), 6 mo PFS为40.1%, 12 mo PFS为21.8%, 中位OS为13.8 mo (11.1 mo-29.3 mo)[103,104]. Lau等[105]应用mTOR抑制剂依维莫司治疗晚期胆管癌, 治疗12 wk时疾病控制率达52%, 中位PFS为5.5 mo, 中位OS为9.5 mo. 但由于ICC肿瘤组织FGFR2、IDH1/2、BRAF-V600E等突变率较低, 目前尚无针对这些分子靶点的广谱分子靶向药物用于ICC及其复发转移的治疗, 其它针对VEGFR、EGFR、CD47等分子抑制剂治疗ICC具有一定疗效, 仍需要多中心临床验证以及深入研究ICC发生发展的确切分子机制, 研发广谱、高效的分子靶向药物是延长术后复发或转移ICC患者生存期的重要措施.

3.8 *免疫治疗* 免疫检查点分子(programmed death 1, PD-1; cytotoxic T-lymphocyte-associated protein 4, CTLA-4)是肿瘤形免疫逃逸的关键机制, 这些检查点被其特定配体(PD-L1、CD152)分别激活, 促进外周血T细胞凋亡, 免疫检查点分子抑制剂能够增强抗肿瘤免疫反应, 杀灭肿瘤细胞[106]. 仅5% ICC存在微卫星不稳定, 对PD-1抗体治疗敏感[107]. PD-L1在17.7%-30.9% ICC中表达, PD-L1上调可能促进ICC细胞的侵袭和迁移, 并对AKT信号有负反馈抑制作用, PD-L1细胞内信号可以保护癌细胞免受干扰素的细胞毒性, 加速肿瘤进展[108,109]. PD-L1分子在ICC肿瘤组织表达显著高于癌旁组织(51.7% *vs* 5 %, *P*<0.05), 不同TNM分期及淋巴结转移PD-L1分子表达亦有差异, 但患者性别、年龄、分化程度和肿瘤直径与PD-L1表达无关[110]. ICC肿瘤组织表达PD-L1表达与ICC患者总生存期降低60%密切相关[111]. PD-1抗体派姆单抗治疗其它治疗失败且具有微卫星不稳定性/错配修复缺陷胆管癌, ORR为40.9%[112]. PD-1抑制剂Toripalimab联合GEMOX(奥沙利铂和吉西他滨)化疗和Lenvatinib治疗晚期ICC的ORR为80%, 疾病控制率为93.3%[113]. Xiong等[114]应用奥拉帕尼和派姆单抗治疗BRCA1突变和PD-L1阳性ICC复发转移, 患者口服奥拉帕尼联合派姆单抗15次治疗, 复发肝内转移肿瘤和淋巴结转移病灶完全消失, 肿瘤标记物正常, 完全缓解9 mo, 收到较好疗效. 王泽阳等[115]应用PD-1抑制剂特瑞普利单抗治疗ICC术后2年复发患者, 一线应用GC方案, PFS为6 mo, 二线应用替吉奥, PFS 为2 mo, 由于患者耐受性差, 三线应用特瑞普利单抗免疫治疗, 6 mo后达到完全缓解, 免疫治疗为术后复发或转移ICC提供较好疗效.

其它如嵌合抗原受体T细胞免疫疗法(CAR-T)、肿瘤疫苗、基因工程疫苗(P53)、过继免疫疗法(CTL细胞、NK细胞、巨噬细胞、 LAK细胞和TIL细胞)等均有一定抗肿瘤作用, 但大多数仍处于临床试验阶段, 需要针对复发或转移性ICC, 通过手术、局部消融、TACE、化疗、放疗、分子靶向药物、免疫治疗等多模式联合治疗手段, 提高复发或转移ICC患者远期生存率.

4 预防

9.5% HBV感染的ICC患者肝切除术后存在乙肝病毒再激活, 而较高的HBV-DNA水平和病毒再激活导致肿瘤复发, 术前抗乙肝病毒治疗可降低HBV感染相关ICC患者术后病毒再激活发生率, 围手术期抗乙肝病毒治疗降低术后肿瘤复发, 使ICC患者生存受益[116]. Li等[117]研究发现肝切除术后辅助TACE能够延长TNM Ⅱ期、Ⅲ期和Ⅳ期ICC患者生存, 但对于TNM I期患者不仅不能延长生存期, 反而促进肿瘤复发, 可能与TACE诱导局部血管生成因子促进肿瘤复发转移的机制有关. 与未接受TACE相比, 高危复发ICC患者(N1、T2/T3/T4期)术后接受辅助性TACE治疗显著提高患者术后无复发生存, 1、3年无复发生存率(48%、27% *vs* 27%、0%), 1、3、5年总体生存率(71%、34%、14% *vs* 41%、0%、0%)(P<0.001); 而低危复发ICC患者术后接受辅助性TACE治疗不能提高患者术后无复发生存, 1、3年无复发生存率(56%、34% *vs* 74%、37%), 1、3、5年总体生存率(68%、32%、21% *vs* 73%、41%、27%)(P>0.05)[118]. 与未行TACE相比, ICC术后肿瘤复发再次根治性切除患者术后行TACE预防性治疗4个周期, 显著降低肿瘤复发率(21.28% *vs* 46.8%, P<0.05), 表明TACE能够有效降低ICC再次术后肿瘤复发率[119]. 多发性肿瘤、肿瘤位于肝门、血清癌胚抗原(CEA)浓度>2.2 ng/mL的ICC患者, 术前进行化疗显著降低术后肿瘤复发与转移[120]. T3/T4肿瘤及N1期的ICC患者辅助性化疗对于改善术后远期生存的作用最强, 术后辅助性化疗适用于肿瘤分期较晚、病理类型为胆管浸润型或肿块+胆管浸润型、存在淋巴结转移的ICC患者[121]. 对于具有复发高危因素(R1切除、血管侵犯、TNM分期Ⅲ期、CA19-9值高)的ICC患者, 术后辅助双药联合化疗方案能显著延长患者DFS[122]. AFP、CEA、CA19-9联合检查预测ICC淋巴结转移的灵敏度、特异度和准确度分别为92.3%、96.3%、95%, 优于AFP+CEA(84.6%、81.5%、82.5%)、CEA+CA19-9(84.6%、85.2%、85%)、AFP+CA19-9(84.6%、88.9%、87.5%)、单一指标AFP(76.9%、74.1%、75%)、CEA(61.5%、70.4%、67.5%)、CA9-9(69.2%、81.5%、77.5%)(P<0.05), 多种肿瘤标志物联合检测有助于指导ICC临床分期、淋巴结清扫和术后辅助治疗[123]. ICC淋巴结转移与T分期密切相关, T1淋巴结转移率为22%-24%(T1a: 24%, T1b: 22%), T2为42.9%-55.3%, T3为48%-51.4%, T4为39%-66%[5,124]. 依据不同T分期, 对ICC患者术中采用个体化淋巴结清扫策略, T1a期淋巴结清扫数目不超过5个, T1b+T2期为6-11个, T3期为4-12个, 不建议对T4期行常规淋巴结清扫[125]. ICC术前是否存在淋巴结转移、术中是否需要进行淋巴结清扫及清扫范围、术后是否需要辅助性TACE、化疗或分子靶向药物等治疗? 仍需要进行多中心、前瞻性研究.

5 结论

由于ICC早期无特征性临床表现, 缺乏早期诊断特异分子标志物, 就诊时多为中晚期, 手术切除率低. ICC生物学行为不同于肝细胞癌, 恶性程度高, 即使手术切除, 术后肿瘤复发转移率高, 放化疗、分子靶向药物和免疫治疗疗效低, 患者预后差. 相信随着对ICC发生发展相关基因、分子病理、影像诊断技术研究深入, 不仅能够提高ICC早期诊断率和精确临床分期, 而且指导选择个体化的精准治疗方案, 是降低ICC术后肿瘤复发与转移率, 改善ICC患者预后的关键.

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