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· 文献综述 ·

结石与非结石性肝内胆管癌肝切除术的围手术期管理差异

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摘要

肝胆管结石是指发生在左右肝管汇合部以上的结石病。该病可引起胆道梗阻及胆汁淤积, 继而增加结石的发生率, 而机械梗阻及反复炎症刺激将加重胆道梗阻, 从而引起一系列严重的并发症, 如胆管炎、肝萎缩、肝硬化等, 甚至诱发胆管癌变。肝内胆管癌 (ICC) 是常见的肝脏恶性肿瘤, 其起源于肝内胆管上皮, 有着恶性程度高、手术根治率低、术后复发率高、预后差等特点, 因此也成为影响国民健康的重大疾病。ICC 的病因目前尚未明确, 众多研究表明, 肝胆管结石是 ICC 的高危因素之一, 在结石长期的机械刺激及慢性炎症刺激下, 胆管上皮沿着增生修复、不典型性增生、癌前病变的方向发展, 并在此基础上, 最终演变成 ICC。因此, 根据致病因素与结石相关程度将 ICC 分为结石性肝内胆管癌 (HICC) 和非结石性肝内胆管癌 (NHICC)。外科手术仍是 ICC 的主要治疗方式, 早期根治性肝切除术可有效提高 ICC 患者的总体生存率, 改善预后。作为肝内胆管结石的高发地区, 近年来 HICC 在我国的发生率也随之攀升, 因而针对 HICC 的综合管理具有十分重要的临床意义。基于上述背景, 本文以 HICC 为中心, 归纳出 HICC 与 NHICC 的围手术期处理要点差异, 以期为 HICC 患者在整个肝切除术的围手术期内提供个体化、精准化的围手术期管理方式, 从而达到提高诊断率、精准治疗、加速康复、改善预后的目的。

关键词

胆管肿瘤; 胆管, 肝内; 胆石症; 肝切除术; 围手术期; 综述
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Differences in perioperative management between patients with hepatolithiasis-associated and nonhepatolithiasis-associated intrahepatic cholangiocarcinoma undergoing hepatectomy

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Abstract

Hepatolithiasis is a type of lithiasis that occurs above the confluence of the left and right hepatic ducts. This condition can cause bile duct obstruction and stasis, increasing the likelihood of stone formation. Mechanical obstruction and recurrent inflammatory stimuli can exacerbate bile duct blockage, leading to

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severe complications such as cholangitis, liver atrophy, cirrhosis, and even the development of cholangiocarcinoma. Intrahepatic cholangiocarcinoma (ICC) is a common malignant liver tumor originating from the intrahepatic bile duct epithelium. It is characterized by high malignancy, low surgical cure rate, high postoperative recurrence rate, and poor prognosis, making it a significant public health concern. The etiology of ICC is still unclear, but numerous studies have indicated that hepatolithiasis is one of the high-risk factors for ICC. Prolonged mechanical and chronic inflammatory stimuli from stones can lead to the development of the bile duct epithelium along the direction of hyperplasia, atypical hyperplasia, and precancerous lesions, eventually evolving into ICC. Based on the degree of association between pathogenic factors and hepatolithiasis, ICC can be classified into hepatolithiasis-related intrahepatic cholangiocarcinoma (HICC) and non-hepatolithiasis-related intrahepatic cholangiocarcinoma (NHICC). Surgical intervention remains the primary treatment for ICC, and early radical hepatectomy can effectively improve the overall survival rate and prognosis of ICC patients. As an area with a high incidence of hepatolithiasis, the incidence of HICC in our country has also been increasing in recent years. Therefore, comprehensive management of HICC is of significant clinical importance. Given the above background, this article focuses on HICC and summarizes the differences in perioperative management between HICC and NHICC. The aim is to provide individualized and precise perioperative management for HICC patients throughout the hepatectomy period to improve the diagnostic rate, provide accurate treatment, accelerate recovery, and enhance the prognosis.

Key words Bile Duct Neoplasms; Bile Ducts, Intrahepatic; Cholelithiasis; Hepatectomy; Perioperative Period; Review

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肝内胆管癌 (intrahepatic cholangiocarcinoma, ICC) 是肝内二级胆管以上部位的胆管恶性肿瘤^[1], 其起源于胆管上皮, 约占原发性肝癌的10%~15%^[2], 在世界范围内发病率和病死率呈上升趋势^[3]。ICC发病隐匿, 较肝细胞癌更具侵袭性, 早期根治性切除是其最有效的治疗方式, 但面临术后复发率极高, 总体预后不佳的困境^[4]。肝内胆管结石好发于远东及东南亚国家, 在西方国家少见^[5]。肝内胆管结石是ICC的高危因素之一, 根据发病与结石相关程度, 将ICC分为结石性肝内胆管癌 (hepatolithiasis-associated intrahepatic cholangiocarcinoma, HICC) 和非结石性肝内胆管癌 (nonhepatolithiasis-associated intrahepatic cholangiocarcinoma, NHICC), 有研究^[6]显示, 5%左右的肝内胆管结石患者在术中诊断为HICC。首先, 两类ICC在术前评估方面存在不同程度的差异, 从而影响整个治疗方案的确定。其次, 目前针对两类ICC的治疗仍是以手术为主的综合治疗模式, 由于HICC与NHICC的肿瘤学特性不同, 因而手术治疗的方式也需要根据肿瘤所在的部位、残肝体积

(future liver remnant, FLR) 等因素进行综合评估, 从而制定适当的治疗方案。最后, 由于两类ICC在术后并发症的发生情况上存在差异, 从而影响着术后的治疗。因此, 对两类ICC在术前评估、术中处理方式、术后治疗整个围手术期的处理策略上进行差异化处理有着十分重要的临床意义。本文通过对国内外该领域相关文献的报道进行总结分析, 归纳HICC与NHICC的围手术期处理要点差异, 为患者提供个体化、精准化的围手术期处理模式提供参考。

1 术前评估

1.1 术前肝病背景评估

ICC的主要致病因素除与结石相关之外, 其他因素还包括病毒性肝炎、原发性硬化性胆管炎 (primary sclerosing cholangitis, PSC)、寄生虫感染等^[7-8]。HICC患者往往合并长期胆管结石的存在, 在结石的反复刺激下患者有长期的急或慢性胆管炎症、感染、脓肿等病史, 亦可导致胆管狭窄、

肝脏萎缩-肥大综合征、胆汁性肝硬化等。HICC常因合并胆道相关感染（如急慢性胆管炎、肝脓肿等）入院，其术中出血及术后感染的风险均会增加，因此对于合并胆道感染的HICC患者在行肝切除术术前评估时应充分考虑结石的分布、肝功能、感染情况，予以积极抗感染、穿刺引流、胆道减压等处理以减轻感染症状及改善肝功能，降低围手术期的风险，并在控制感染后限期行根治术；对于NHICC患者评估时应着重注意患者是否有PSC、寄生虫感染、病毒性肝炎等病史以与HICC相鉴别。通过术前准确评估不同类型肿瘤患者的疾病背景，综合肝功能、凝血功能、肝功能Child-Pugh评分、吲哚菁绿（ICG）清除率、FLR等指标，术前评估是否需要护肝处理，可有效延缓病情的进程，从而保障围手术期的安全性，以期提高生存质量及改善预后的目的^[9]。

1.2 术前影像学评估

ICC缺乏特异性临床表现，影像学检查是术前诊断、制定手术方式和评估手术难度的重要方式。术前影像学评估以B超、CT和MRI、PET/CT、三维可视化为主^[10]。ICC在超声上表现为低回声占位或胆道扩张；增强CT及MRI是诊断ICC的重要影像学检查，由于ICC为乏血供肿瘤，典型增强CT表现为平扫期肝脏不规则低密度占位，动脉期肿瘤周边强化，动脉期至静脉期肿瘤逐渐强化，而延迟期进一步强化^[11]。除此之外，HICC可见点片状高密度结石影并伴随有肝叶萎缩征象，NHICC多具有肝硬化背景，多数表现为类似肝细胞癌的增强模式，易与肝内其他恶性肿瘤相混淆^[12]。MRI检查中两种类型的ICC特征与CT上的表现类似，由于肝内胆管结石的存在，CT相较于MRI对HICC的诊断更直观，此外，CT在确定动静脉受累方面精度更高，而MRI具有良好的软组织分辨率及多参数成像的优势，因而联合CT及MRI的影像学检查可提高对HICC的诊断率，而磁共振胆胰管成像（magnetic resonance cholangiopancreatography, MRCP）可显示肝内胆管的走行，并可直接显示结石、ICC的部位，可与胆管外肿瘤相鉴别，同时明确胆管与肿瘤的相互关系^[13]，为手术方法的制定提供参考。PET/CT在评估肿瘤代谢上具有优势，能显著提高诊断的准确性。PET/CT对ICC诊断的敏感度达90%，可发现20%~30%的隐源性播散情况，并可在术前提供较为准确的淋巴结转移情况，术前提

期更精准，从而影响ICC患者的整体治疗方案，但PET/CT存在价格昂贵、放射性污染等问题，建议在常规影像学检查提示有转移征象的ICC患者可行PET/CT检查以明确是否存在局部及远处转移情况^[14]；三维可视化在术前诊断与术中规划发挥极为关键的作用^[15]，可清楚地显示肿瘤位置、浸润范围、胆管及血管有无变异、胆管狭窄程度和范围、肝脏有无萎缩等，对于HICC患者还能明确结石的大小及分布情况^[16]。充分的影像学评估在ICC的术前准备中是必要的，术前精准定位病灶，根据病变部位做出肝切除方式及范围的决策和对保证术中、术后的安全性具有重要的意义。

1.3 病理学及分子诊断的差异

HICC较NHICC缺乏典型的临床症状，无特异度及敏感度高的检查手段，早期诊断困难，远期预后差^[17]。两类ICC在发生部位、免疫组化、基因组学特点上存在不同。在结石的长期刺激下，胆管上皮细胞增生发展为不典型增生及腺瘤癌变是HICC的病理过程^[18]。HICC常发生于肝内较大胆管上皮，而NHICC常发生于肝内小胆管^[19]。近年来，关于ICC的生物分子诊断有很大突破，多个生物分子及信号通路参与ICC的发生发展及侵袭转移，同时也为ICC的诊断及治疗带来新的靶点^[20]。有研究^[21]显示黏蛋白3（mucin-3, MUC3）及黏蛋白4（mucin-4, MUC4）与HICC的进展、侵袭及转移紧密相关；通过检测HICC组织中MUC3和MUC4的表达程度，可判断HICC患者预后。此外，检测p16基因启动子甲基化可作为早期诊断HICC的指标^[22]。但目前尚无特异的血清生物标记物能准确诊断ICC，临床上联合CA19-9和CEA^[23-24]对ICC的诊断有指导意义。此外，CA19-9还可作为ICC患者评估预后的指标之一，有研究^[25]表明术前CA19-9升高是影响ICC患者术后生存的独立危险因素，因此通过检测患者的CA19-9水平还可对患者的生存状况进行预测。

2 术中处理

2.1 肝切除术手术方式要点差异

2.1.1 肝切除范围及淋巴结清扫要点差异 肝切除术是ICC患者手术治疗的标准术式，基于术前检查确定肿瘤部位及FLR制定合适肝切除范围，由于ICC常沿胆管浸润，因此多推荐半肝切除术或扩大

肝切除术,尽可能达到切缘阴性^[26-27]。HICC患者在术中既要保证肿瘤的根治原则,还需要取尽肝内结石^[28-29]。受肝内胆管解剖学的影响,肝内胆管结石好发于肝左叶,故HICC患者的病变常发生在左半肝,因此术中在保证切缘阴性的前提及足够的FLR情况下,若能达到 ≥ 1 cm的手术切缘宽度则可改善患者生存情况从而使其获益^[30]。NHICC常合并病毒性肝炎,左、右半肝均可发生,行肝切除时要根据肿瘤的部位、大小,肿瘤是否毗邻胆管,是否侵犯血管,综合患者肝硬化程度,肝功能评估等具体情况,选择合适的切肝范围。既往关于ICC是否常规行淋巴结清扫仍存在争议,争议点为常规淋巴结清扫能否使患者获益^[31-32]。支持观点者认为,对有淋巴结转移者行淋巴结清扫能延长患者生存期^[33];但有研究^[34]表示,伴有淋巴结转移的ICC患者转移区域常超过肝十二指肠韧带,单纯手术切除面临清扫不彻底的风险且不能使患者生存获益。目前研究^[35]表明,ICC患者中有45%~65%伴有淋巴结转移,常规淋巴结清扫有助于对肿瘤进行更为精准的分期,从而判断预后及评估术后是否需要联合化疗,目前有多个共识及指南^[11, 36-39]建议行区域淋巴结清扫并对范围进行阐述。对于确诊ICC的患者均建议根据肿瘤的部位常规行区域淋巴结清扫,并根据情况行扩大清扫,而对于术中无法明确是否存在淋巴结转移可经快速冷冻活检以明确从而降低Nx的状态,实现对ICC的准确分期^[13]。

2.1.2 开腹及微创手术要点差异 既往微创肝切除术治疗ICC报道相对较少,随着外科医生经验的积累、手术设备器械的更新,目前认为所有肝段肿瘤均可通过腹腔镜切除^[40]。与传统的开腹手术相比,腹腔镜手术具有并发症较少、恢复快、微创等优点^[41-42]。且有研究^[43]表明,腹腔镜治疗ICC的R₀切除率更高。随着医疗技术的进步,既往腹腔镜肝切除术治疗ICC面临淋巴结清扫数目不足的窘境也得到改善^[44-45],但在患者的选择上,腹腔镜肝切除术不适用于多发、巨大的ICC患者^[46]。此外,关于气腹是否能促进肿瘤细胞的转移这一观点仍有争议^[47],并且由于腹腔镜器械精细程度及灵活度的限制,也增加了手术的难度。机器人手术具有高清晰度、高灵活性、高稳定性的特点,在困难部位的肝切除术(如尾叶、右后叶切除)上具有明显的优势,且在长期预后效果上可获得与开

放治疗同等的效果^[48]。HICC患者需要保证同时根治肿瘤及结石,当结石与肿瘤在同一肝段及肝叶,且肿瘤位于肝脏较为浅表位置时,微创手术疗效更加显著^[49];而肿瘤位于肝脏膈面、位置深的肝段或与大血管相邻时,腔镜手术的操作难度将会增加,从而增加手术风险^[50]。当结石分散且术前评估FLR不能满足扩大切除术,需联合胆道镜或硬镜取石,以期达到肿瘤根治及胆石治疗原则时,开腹更有利于手术操作,以达到取尽结石的目的。NHICC患者只需考虑肿瘤的根治性原则,微创手术具有视角优势,更容易实施区域淋巴结清扫^[51],故对于肿瘤位置较好,大小合适、既往无腹部手术史的患者选择微创手术疗效更佳。综上所述,手术方式的选择应根据肿瘤的类型、既往是否有腹部手术史、肝切及淋巴结清扫范围等多种因素决定。

2.2 肝切除术中要点

肝切除一般包括肝血流阻断、肝门解剖及肝实质离断三个步骤。ICC因致病因素、治疗目的的不同,在肝切除术三个关键步骤的选择上亦存在一定差别。

2.2.1 肝血流阻断要点 出血量的控制是成功实施肝切除术和降低手术并发症发生率及病死率的关键^[52]。预防出血的最关键技术是入、出肝血流阻断控制,尤其是入肝血流阻断。目前入肝血流阻断常用的方式包括全入肝血流阻断法和区域入肝血流阻断法^[53]。因NHICC患者通常发生胆道梗阻的概率低于HICC患者,其术前的肝功能优于HICC的患者,采用全入肝血流阻断技术可以快速阻断第一肝门,无须过多解剖肝十二指肠韧带,操作简便易行。HICC通常发生在左肝,通常选择行左半肝切除或扩大左半肝切除,选择区域性入肝血流阻断,肝脏表面会形成明显的缺血线,可有助于明确肝实质离断的层面,同时可以避免健侧肝实质发生缺血再灌注损伤,减少术后肝衰竭的发生,同时也避免了由于胃肠道淤血、黏膜屏障受损所致的肠内细菌及内毒素移位,从而降低整个围手术期的风险。此外,在术中超声的引导下也可精准定位肝动脉及门静脉从而实现区域血流的精准阻断,但HICC患者由于长期炎症刺激,局部炎症纤维化可导致第一肝门结构解剖困难,因此需根据患者术中情况、肝切除及淋巴结清扫范围等因素,选择适合患者的个体化入肝血流阻断方

式, 以达到缩短手术时间、减少术中出血量从而保障整个围手术期的安全性^[54]。

2.2.2 肝实质离断要点 肝实质离断是肝切除手术的重要关键步骤, 重点在于出血的预防及处理, 精准解剖处理管道是关键。HICC患者由于结石的长期刺激, 常伴肝脏萎缩肥大综合征、肝硬化等基础肝病背景, 因而伴有肝内脉管解剖移位, 增加整个围手术期的风险。术中超声实时监测对深埋于肝实质内部的肿瘤具有定位的作用, 可精确识别肝内重要血管及胆管从而避免损伤, 在超声引导下还可识别肝胆管内残余的结石, 术中结合胆道镜取石等方式可有效降低残石率^[55]。三维成像技术可在术前清晰显示肿瘤部位及其与周围脉管的关系, 也可清楚显示肝内胆道走形及结石分布, 对胆道变异的诊断也具有帮助, 从而减少术中医源性损伤的风险^[56]; 此外, 三维成像技术可模拟肝切除方案, 并计算FLR, 从而避免过度肝组织切除术后肝衰竭的风险。ICG荧光显影技术对HICC手术也具有重要的临床意义, 经静脉或胆道注射ICG后借助荧光设备可清晰显示胆道的走形情况, 借助显像部位也可明确HICC的梗阻部位。若怀疑术中有胆道损伤, 经胆道注射ICG也可协助胆汁漏的诊断^[57]。此外, 术中胆道造影、术中联合胆道镜检查对变异胆道的诊断、胆道狭窄的明确均具有帮助。在精准肝脏外科理念不断发展的背景下, 综合术前、术中检查或是多种术中引导技术的联合使用可有效降低HICC患者的手术风险、保障围手术期安全、加速术后康复过程及改善预后。

3 术后并发症

3.1 术后肝衰竭的差异

术后肝衰竭是原发性肝脏恶性肿瘤肝切除术最严重的并发症, 发生率为2.4%~13.9%, 占术后总病死率的18%~75%^[58-59], 肝切除术后肝衰竭与病毒性肝炎、肝硬化、术中出血量及输血量、肝切除范围及术后FLR不足等多种因素相关^[60], HICC患者因结石的存在, 炎症、结石阻塞可导致胆汁性肝硬化, 影响术后肝功能的恢复, 在行扩大肝切除时需要保证患者有足够的FLR^[61-62], 若残石无法取尽, 必要时可留置T管, 术后经T管窦道取石从而避免盲目扩大肝切除导致术后肝衰竭的

发生, 对于存在结石而未行肝切除术的ICC患者需定期随诊, 警惕继发ICC的可能^[63]; 在术后管理上应定期检测肝功能、凝血功能等指标以尽早发现肝功能衰竭, 并及时给予对症护肝处理, 必要时可行人工肝支持治疗, 同时需对可能继发的情况(如肝性脑病、肝肺综合征、肝肾综合征等)进行严密检测, 以达到早期发现及时干预治疗, 保障术后的安全。

3.2 术后胆汁漏的差异

伴随手术技术的进步及围手术期管理的优化, 肝切除术后的安全性已得到明显的改善。虽然肝切除术后的病死率约3%, 但肝切除术后的并发症发生率仍高达30%~40%^[64-65], 由于胆管炎及结石的刺激导致胆管异常等, HICC患者术后胆汁漏发生率极高^[66]。在HICC术后发生胆汁漏时, 根据引流液胆红素或腹腔穿刺物为胆汁可明确诊断, 结合ERCP、经皮肝穿刺胆道引流术等检查可明确胆汁漏的部位及类型。B级胆汁漏为临床上常见的类型, 明确诊断后可在内镜下行鼻胆管引流或支架植入术以减轻胆道压力, 缓解症状; C级胆汁漏提示胆管损伤严重, 往往需要二次手术探查明确原因后行确切治疗。除外, 抗生素治疗及营养支持等也是治疗胆汁漏的有效手段。

3.3 术后一般并发症的差异性

术后感染可继发于胆汁漏。此外, 高龄、术前白蛋白<35 g/L, 术中术野清洗不充分也是术后感染的独立危险因素^[67]。对于伴体内感染的HICC患者术后伤口感染、膈下感染及胆汁漏的风险均随之增高, 且增加术中出血的风险。术后感染影响患者术后的康复过程, 且严重的术后感染会增加术后病死率。对于存在上述危险因素的患者须对术后感染指标进行严密监测, 对怀疑已发生的感染可行血液、引流液等体液培养, 尽早选用合适敏感的抗生素以达到控制感染的目的。此外, 术后出血、胸腹腔积液也是HICC患者术后常见的并发症。通过引流液形状及量的观察、术后CT的复查情况等方式, 做到对并发症的早期诊断并及时干预, 可有效防止并发症进一步恶化及加速患者术后康复过程。

4 小结

ICC具有侵袭性强、高度恶性的特点, 根治性

手术仍然是唯一可能治愈的主要治疗措施,但当前ICC的预后还是不容乐观^[68-69]。因其肝病背景、影像学特点、肿瘤侵袭性及发病机制等方面的不同,HICC与NHICC的患者在术前、术中及术后的围手术期诊疗中存在较大的差异性,作为肝脏外科医师,需要熟练掌握两类ICC的处理要点,通过制定合理的围手术期管理方案,为保障ICC患者围手术期安全及提高术后5年生存率提供精准的医学诊疗思路及技术支持。

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