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肝门部胆管癌的治疗现状及进展

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摘　要

肝门部胆管癌是一种少见的高度侵袭性胆道肿瘤，发病隐匿，恶性程度高，预后较差，手术切除是目前唯一的根治性治疗方法。随着医疗技术的进步及手术水平的提高，患者根治切除率及术后生存率有所提高，但整体治疗效果仍不佳。本文就肝门部胆管癌的治疗现状及进展作一概述。

关键词

肝门部胆管癌，手术切除，姑息治疗

Treatment Status and Progress of Hilar Cholangiocarcinoma

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Abstract

Hilar cholangiocarcinoma is a rare highly invasive biliary tumor with concealed onset, high malignancy and poor prognosis. Surgical resection is the only radical treatment at present. With the progress of medical technology and the improvement of operation level, the radical resection rate and postoperative survival rate of patients have improved, but the overall treatment effect is still poor. This paper summarizes the current situation and progress of the treatment of hilar cholan-

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giocarcinoma.

Keywords

Hilar Cholangiocarcinoma, Resection, Palliative Treatment

1. 引言

肝门部胆管癌是发生于胆管上段的恶性肿瘤，在解剖学上是指左右肝管以下、胆囊管开口以上的肝门区。它是胆管癌最常见的类型，约占所有胆管癌的 50%~70% [1]。肝门部胆管癌是腹部外科治疗难度较大的恶性肿瘤，其原因在于：1) 发病隐匿，多数患者就诊时已是中晚期，丧失了手术机会。加之其特殊的解剖位置，带来了与之相应的手术难度。部分患者的肿瘤沿胆管向左、右肝内胆管生长，导致肿瘤无法根治性切除。只有不到 30%的肝门胆管癌患者能够获得根治性切除的机会[2] [3]。2) 肿瘤的恶性程度高，易发生肝内及周围的浸润转移，远期生存时间较差。对于转移性或不可切除性疾病患者的中位生存期少于 1 年[4]，而对于根治性切除的患者，R0 切除率约为 50%~92%，但五年生存率仍只有 20%~42%，总体五年生存率不足 10% [5] [6]。鉴于肝门胆管癌的特殊性，本文就肝门部胆管癌的治疗现状及进展进行综述。

2. 术前减黄

肝门部胆管癌多以梗阻性黄疸为主要表现，术前减黄目前仍存在争议。梗阻性黄疸会影响肝细胞的功能和肝细胞的再生能力，此外，梗阻性黄疸的患者的肠道屏障功能受损，增加了细菌移位的风险。部分梗阻性黄疸患者术前可能合并胆管炎和脓毒血症，将会增加术后发病率和死亡率[7] [8]。有相应的研究证实，术前减黄有助于减少肝门部胆管癌患者手术后并发症的发生率[9] [10]。但也有反对者认为，术前减黄存在胆道感染的风险和肿瘤种植转移的可能性。有研究表明，与未进行引流的患者相比，剩余肝体积小于 30%的患者术前胆道引流有利于患者术后恢复，而在剩余肝体积较大的患者中，术前胆道引流与较高的死亡率和死亡率呈正相关[11]。因此，美国肝胆胰学会的专家共识认为，合并胆管炎、预计需行半肝以上大范围肝切除、接受新辅助化疗、术前行门静脉栓塞的病人，建议术前行胆道引流[12]。目前胆道引流的方式主要有经皮肝穿刺胆道引流和经十二指肠镜胆道引流两种方式，两种方式各有优缺点。经皮肝穿刺胆道外引流可在超声引流下选择需要引流的目标胆管，可多根胆管引流，减黄效果确切。但存在出血、胆瘘、肿瘤种植转移、穿刺引流管脱落等风险。大量胆汁引流至体外，会导致消化功能障碍、水电解质平衡紊乱。经十二指肠镜途径的鼻胆管引流(ENBD)也具有确切的减黄效果，但患者具有明显的不适感[13]，同样也存在胆汁外引流后所致的肠道营养吸收功能障碍、水电解质平衡紊乱等缺点。经内镜途径胆道支架内引流可避免胆汁的丢失，更符合正常胆道的解剖及生理功能。但经内镜途径的内引流和外引流(ENBD)方式均有术后胆管炎、急性胰腺炎等并发症发生的风险[14]，并且会导致肝十二指肠韧带的炎症水肿，从而增加手术难度。因此，应该根据肝门部胆管癌的分型选择相应的胆道引流方式。一般认为，Bismuth Corlette III、IV 型肝门部胆管癌因其梗阻位置较高，经内镜途径难以超选至目标胆管，引流成功率低、引流效果差，更适合行经皮穿刺肝胆管引流[15]。

3. 手术切除

3.1. 切除范围

手术切除是肝门部胆管癌的重要治疗手段，手术方式已经从简单的姑息性胆管切除术发展到精准的肝切除术，并伴随着发病率和死亡率的显著降低。根治性手术目前仍是肝门部胆管癌治愈的唯一途径[16]。中国 2015 版肝门部胆管癌规范化诊治专家共识指出，根治性切除的范围包括：肝门部及胰腺上肝外胆管、区域淋巴结、部分肝脏(包括尾状叶)的整块切除[17]。具体切除范围根据患者的肿瘤 Bismuth-Corlette 分型而选择。I 型和部分 II 型行肝外胆管、胆囊切除 + 区域淋巴结清扫 + 肝管空肠 Roux-en-Y 吻合术；部分 II 型行小范围肝切除 + 尾状叶切除 + 区域淋巴结清扫 + 肝管空肠 Roux-en-Y 吻合术；III 型肝门部胆管癌需切除左或右半肝并联合尾状叶切除 + 区域淋巴结清扫 + 肝管空肠 Roux-en-Y 吻合术；IV 型无法切除采取肝移植或非手术治疗。

对于行根治性切除的肝门部胆管癌患者来说，手术切缘阴性(R0 切除)是影响患者预后的一个重要独立因素[18] [19]，因此，在手术中需切除足够长度的胆管以保证手术切缘的阴性。但对于肿瘤位置较高的患者，需联合半肝的切除，并经过高位胆管整形后才能完成胆肠吻合。所以在保证 R0 切除的同时，还需兼顾实施胆肠吻合的成功性。研究表明，尾状叶胆管因为距离肝门较接近而更易受肿瘤浸润转移，因此，行肝切除术时主张联合尾状叶切除[20] [21]。但肝门部胆管癌患者往往合并梗阻性黄疸及肝功能损害，大范围的肝切除导致患者术后发生肝功能衰竭的可能性增加。王曙光教授等提出行“哑铃式”肝门胆管癌根治性切除术，切除范围包括肝 IVb 段、部分肝 V 段、肝尾状叶(肝 I 段)、左右肝管及肝外胆管。因该术式切除的组织标本形体上如哑铃状，故被称之为“哑铃”式肝门部胆管癌根治术[22]。该术式既切除了尾状叶的切除，保证了 R0 切除，又兼顾了剩余足够的肝体积，避免术后肝功能衰竭等并发症。

3.2. 淋巴结清扫

既往研究表明，肝门部胆管癌发生淋巴结转移的机率为 30%~60% [23]，而伴有淋巴结转移的患者术后 5 年生存率(<20%)明显低于不伴有淋巴结转移的患者(30%~46%) [24] [25] [26]。淋巴结转移和 R0 切除目前被认为是影响肝门部胆管癌患者手术切除预后的独立危险因素[19] [27]。此外，淋巴结清扫有助于判断患者的肿瘤分期，因此，国内外对于肝门部胆管癌根治术的术式已达成共识，即行 R0 切除并联合淋巴结清扫。但具体淋巴结清扫范围与是否需行扩大的淋巴清扫术目前仍存在争议。支持行扩大淋巴结清扫的学者认为，对于存在区域淋巴结转移的肝门部胆管癌患者，扩大淋巴结清扫范可提高患者术后生存时间，并可以提供更准确的瘤分 期信息[28] [29]。反对扩大淋巴结清扫的学者认为，扩大的淋巴结清扫术带来更大的手术创伤，但对患者的术后总生存时间并无改善[30]。我国 2015 年制定的《肝门部胆管癌规范化诊治专家共识》建议行 R0 切除的同时行肝十二指肠韧带淋巴结(N1)和肝总动脉旁、胰腺后上方淋巴结(N2)的区域淋巴结清扫，而不常规行腹主动脉旁、腹腔干旁、肠系膜上动脉根部和胰腺前方等淋巴结的扩大清扫[17]。

3.3. 血管切除及重建

因解剖学特性，肝门胆管癌易侵犯毗邻的肝动脉及门静脉。因此，部分肝门胆管癌的患者要想达到 R0 切除，则需联合血管切除并重建。既往观点认为联合血管切除重建的肝门部胆管癌根治术的手术难度大，手术风险高，甚至把肿瘤侵犯肝动脉或门静脉认为是行根治性手术的禁忌[31]。但随着外科医生手术技术的进步，血管切除并重建已经证实是安全可行的。日本横滨大学对 172 例肝门部胆管癌患者的研究中发现，行肝动脉或门静脉切除重建与未行血管切除重建的患者术后并发症的发生率差异无统计学意义

[32]。患者是否能通过血管切除重建而获益目前仍存在争议。一部分学者认为，通过血管切除并重建，可以延长患者的生存时间并改善预后[16] [33]，但也有大量研究认为联合血管切除并重建并没有改变患者的总体生存时间和无瘤生存时间[34] [35]。因此，联合血管切除重建虽不作为肝门部根治术的常规推荐，但却为患者的根治性切除提供了更多的选择。

3.4. 腹腔镜技术的应用

微创是外科发展的趋势，肝门部胆管癌根治术虽然手术复杂、难度大，但仍然不是腹腔镜微创手术的禁区。腹腔镜肝门部胆管癌根治术也从最初的肝外胆管切除到联合全尾状叶的扩大半肝切除术 + 区域淋巴结清扫，手术切除的范围及预后与开放性手术无差异，但腹腔镜手术的手术时间更短、失血更少、并发症发生率更低[36] [37] [38]。甚至对于部分 III 型、IV 型等难度较大的患者仍可行腹腔镜手术，并且证实是安全可靠的[39]。但胆漏发生的机率腹腔镜肝门部胆管癌根治术高于开放性手术，这与腹腔镜下行胆肠吻合操作的局限性有关。特别是对于 III 型、IV 型肝门部胆管癌患者来说，因肿瘤切除后待吻合的胆管直径较细，位置较深，腔镜缝合空间局限[40]。总的来说，腹腔镜肝门部胆管癌根治术属于难度大、风险高的手术，需要严格掌握适应证，选择合适的病例。我国腹腔镜肝门部胆管癌根治性切除操作流程专家建议(2019 版)指出，对于 I 型、II 型的患者可在腹腔镜下完成切除及重建；对于部分 III 型、IV 型患者可行腹腔镜手术，但如肿瘤侵犯门静脉或肝动脉，则建议开腹手术行血管切除重建或行姑息性治疗等相应处理[41]。

3.5. 肝移植

根治性手术切除一直是肝门部胆管癌的主要治疗方法，但对于肿瘤较晚期或者剩余肝体积不足的患者来说，肝移植无疑是一种最好的选择。但最初阶段肝移植的效果并不佳，5 年生存率为 23%，复发率高达 50%以上，其中 84%的病人 2 年内复发[42]。美国梅奥诊所将新辅助化疗与肝移植相结合，以治疗无法根治性切除的患者。他们在 2005 年发表的随访结果报告了 38 名正在进行肝门癌肝移植的患者，5 年生存率为 82% [43]。与手术切除的患者相比，移植患者的生存率更好，复发率更低。他们近期的研究还证实，原发性硬化性胆管炎相关的肝门胆管癌的效果优于新生型肝门胆管癌患者(5 年存活率 74% VS 58%，5 年复发率 22% VS 45%) [44]。在梅奥诊所结果的推动下，其他中心也开始了肝门胆管癌的肝移植研究。Ethun 等人通过多中心的研究结果证实，在这些医疗中心，接受肝移植的患者的 5 年生存率(64% VS 18%)高于行根治性切除的患者。他们的研究还证实，在肿瘤较小且区域淋巴结阴性的肝门胆管癌患者行肝移植，5 年生存率更高[45]。Zaborowski 等根据梅奥团队的经验进行了单中心的回顾性研究，26 例肝门胆管癌患者接受了新辅助化疗后完成了肝移植术，术后 1，3，5 年存活率分别为 81%，69%和 55%，获得病理完全缓解患者的中位生存期为 83.8 个月，残余肿瘤组患者的中位生存时间为 20.9 个月，总体中位生存时间为 53 个月[46]。

但是，由于供肝短缺、治疗费用昂贵，目前在我国无法大规模地开展肝移植手术，因此该术式有比较大的局限性。

4. 总结

手术切除虽然是治疗肝门部胆管癌的主要方法，但对于不可切除的肝门部胆管癌，姑息性治疗可以减轻患者症状、延缓病情、延长患者生存时间。针对患者梗阻性黄疸，可采取经皮肝穿刺胆管引流、经皮或经内镜胆道支架植入以减黄。针对肿瘤本身，可采取经内镜胆道射频消融、光动力治疗、放疗等减瘤方式。此外，全身化疗、靶向治疗和免疫治疗也证实对肝门胆管癌有一定的效果[47] [48]。肝门部胆管

癌同其他肿瘤一样，需要多学科、个体化、综合性治疗。尽管目前的手术治疗和姑息性治疗效果都不尽人意，但相信随着医疗技术的不断进步，肝门胆管癌患者的生存时间将进一步延长，患者生活质量得到进一步的提高。

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