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Hans汉斯

肝门部胆管癌的内镜诊疗研究进展

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摘　要

肝门部胆管癌(hilar cholangiocarcinoma, HCCA)属于一类恶性程度较高、侵袭性显著的肿瘤性疾病，发病率逐年上升，预后较差。由于其解剖位置复杂、早期缺乏特异性症状，临床诊断与治疗面临挑战。近年来，内镜相关技术的不断发展为HCCA的精准诊断与综合治疗提供了新的思路与手段。本文系统综述了HCCA在内镜诊疗方面的最新进展，涵盖内镜逆行胰胆管造影与胆管内超声的协同应用、SpyGlass与国产胆道镜系统的对比、超声内镜引导下细针穿刺抽吸/活检在组织学诊断中的突破、荧光原位杂交等分子病理技术的引入，以及多种内镜下胆道引流和胆管腔内治疗方式的临床实践。在诊断方面，新兴内镜技术显著提高了病灶识别与组织获取的敏感性与准确性；在治疗方面，个体化引流策略和局部腔内治疗手段拓展了HCCA的综合管理路径。未来，随着人工智能、精准介入及影像引导技术的融合，HCCA的内镜诊疗将朝着更微创、更精准、更个体化的方向发展。

关键词

肝门部胆管癌，内镜诊断，胆道引流，内镜局部治疗

Advances in Endoscopic Diagnosis and Treatment of Hilar Cholangiocarcinoma

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Abstract

Hilar cholangiocarcinoma (HCCA) is a highly aggressive malignancy with increasing global incidence and poor prognosis. Due to its anatomically complex location and lack of specific early symptoms, both diagnosis and treatment remain challenging. In recent years, the continuous advancement of

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endoscopic techniques has provided new strategies for the accurate diagnosis and comprehensive management of HCCA. This review systematically summarizes recent progress in endoscopic diagnosis and therapy for HCCA, including the combined application of ERCP and intraductal ultrasound, comparison between SpyGlass and domestic cholangioscopy systems, breakthroughs in histological diagnosis using EUS-guided fine-needle aspiration/biopsy, the incorporation of molecular techniques such as fluorescence in situ hybridization, and various endoscopic biliary drainage and intraductal therapeutic approaches. In terms of diagnosis, novel endoscopic modalities have significantly improved the sensitivity and accuracy of lesion identification and tissue acquisition. Therapeutically, individualized drainage strategies and local ablative therapies have expanded the treatment landscape for HCCA. With the integration of artificial intelligence, precision interventions, and image-guided technologies, endoscopic diagnosis and treatment of HCCA is expected to move towards a more minimally invasive, accurate, and personalized era.

Keywords

Hilar Cholangiocarcinoma, Endoscopic Diagnosis, Biliary Drainage, Endoscopic Local Therapy

1. 疾病概述与诊疗挑战

1.1. 流行病学与临床特征

肝门部胆管癌(hilar cholangiocarcinoma, HCCA)是起源于肝门部胆管黏膜上皮的恶性肿瘤，其解剖定位为胆囊管与胆总管汇合处至二级胆管起始部之间的胆管系统，占胆道恶性肿瘤的 50%~70%，居肝外胆管癌首位[1]-[3]。HCCA 好发于 50~70 岁中老年人群，男性略多于女性(性别比 1.2~1.5:1) [4]-[6]。流行病学数据显示，近十年全球 HCCA 发病率与死亡率持续攀升，其疾病负担日益加重，尤以东南亚地区最为显著。我国作为 HCCA 高发区域，发病率显著高于欧美国家(欧洲/北美/澳大利亚：0.35~2/10 万；泰国东北部：85/10 万) [7]。HCCA 发病危险因素存在显著地域异质性：欧美患者多继发于原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)，而东南亚地区约 60%的病例与华支睾吸虫慢性感染相关。此外，胆管结石病、胆管囊状扩张症等胆道结构异常亦被证实显著增加 HCCA 发病风险[8]-[10]。HCCA 早期缺乏特异性临床表现，约 30%患者通过肝功能异常或影像学检查偶然发现，疾病进展期以进行性无痛性黄疸为典型特征[11]-[13]。目前尚无针对 HCCA 的特异性血清标志物，临床上多依赖糖类抗原 19-9 (carbohydrate antigen 19-9, CA19-9)与癌胚抗原(carcinoembryonic antigen, CEA)的联合检测来辅助判断。约 85%患者 CA19-9 水平 ＞37 U/mL (临界值)，但其敏感性与 Lewis 血型抗原表型密切相关，约 10%的 Lewis 抗原阴性个体因基因缺陷无法合成 CA19-9，可能导致假阴性结果[14]。

1.2. 诊疗困境与需求

由于肝门部结构复杂，HCCA 常累及该区域的关键血管、神经丛、淋巴结以及邻近肝实质，使得临床治疗面临诸多挑战，整体预后较差。特别是对于失去手术机会的患者而言，其五年生存率通常低于 20%。目前来看，根治性外科切除仍被视为唯一有可能实现治愈的治疗策略[15]。然而，由于患者早期缺乏特异性临床表现，且肿瘤具有高度侵袭性，多数患者确诊时已处于中晚期，约 2/3 的 HCCA 患者在确诊或手术探查时即为不可切除。即使在接受根治性切除后，术后复发率仍高达 60%~70% [16]。早期的诊疗手段

主要依赖传统影像学检查及经皮穿刺取样，存在定位不准、获取组织有限等问题。近年来，随着内镜相关技术的不断进步，诸如内镜逆行胰胆管造影(endoscopic retrograde cholangiopancreatography, ERCP)、超声内镜(endoscopic ultrasound, EUS)、在超声内镜引导下进行的细针穿刺抽吸或组织活检(endoscopic ultrasound-guided fine-needle aspiration/biopsy, EUS-FNA/B)、胆道内超声(intraductal ultrasound, IDUS)以及荧光原位杂交(fluorescence in situ hybridization, FISH)等检查手段相继应用于临床。内镜技术在 HCCA 管理中从最初的辅助引流手段，逐步演进为集诊断、定位、活检、分期、减黄及局部治疗于一体的综合诊疗平台。其在 HCCA 管理中从最初的辅助引流手段，逐步演进为集诊断、定位、活检、分期、减黄及局部治疗于一体的综合诊疗平台。

2. 诊断技术创新

2.1. ERCP 与 IDUS 的协同应用

ERCP 可以直观地显示胆道狭窄或梗阻部位，并同时进行刷检或活检钳活检。然而，ERCP 单独应用时诊断敏感性有限，约 40%~70% [17] [18]。IDUS 是在 ERCP 引导下经胆管或胰管置入高频超声探头，以实时获得管腔内部及周围组织的高分辨率超声图像。典型的恶性病变在超声下常呈现出胆管壁层次结构紊乱甚至消失、管壁偏心性增厚，并可见界限模糊、回声低而分布不均的病灶向周围组织浸润，常同时伴有区域性淋巴结肿大。相比之下，良性狭窄通常显示为胆管壁结构规则分明，轮廓平整，回声分布均匀，未见明显侵犯周围组织的表现[19] [20]。与 ERCP 引导的组织获取相比，IDUS 对于胆管狭窄具有更高的灵敏度(90% vs. 48%)、阴性预测值(90% vs. 64%)及准确率(92% vs. 73%) [21]。ERCP 联合 IDUS 可显著提高胆道恶性病变的诊断效能。Meister 等[22]对 397 例患者的回顾性分析表明，ERCP 联合 IDUS 诊断胆道恶性病变的敏感性为 93.2%，特异性为 89.5%，诊断准确率达到 91.4%。一项荟萃分析[23]研究表明，将 ERCP 与 IDUS 联合应用于胆管狭窄性质的判断时，其诊断敏感性达 96.9%，特异性为 79.2%，整体准确率为 88.1%。在对比不同部位胆管狭窄的诊断表现时，近端病变的识别准确性明显优于远端(98.08% vs. 82.73%, P = 0.006)。此外，联合使用的诊断效果显著优于单独依赖 ERCP、EUS 或计算机断层扫描(computed tomography, CT)。另一项由 Kim 等人开展的研究[24]进一步指出，在 IDUS 引导下配合 X 线定位进行组织活检，其诊断准确率为 90.8%，明显优于传统 ERCP 活检方式(76.9%, P = 0.005)。另有研究指出，IDUS 对胆管肿瘤的局部 T 分期能力也明显优于传统的 EUS (准确率 77.7% vs. 54.1%)，但对淋巴结转移的诊断能力受限(准确率 33.3%) [25]。然而，IDUS 联合 ERCP 具有一定风险，多项研究将其明确为 ERCP 术后胰腺炎的独立危险因素，尤其在技术操作经验不足的情况下，需谨慎应用[26] [27]。

2.2. 胆道镜技术的革新

2.2.1. SpyGlass 系统

SpyGlass 是一种单人操作的经口胆道镜系统，使操作者能够在进行 ERCP 过程中，直接目视胆道内壁形态变化，并借助专用的 Spybite 微型钳精准获取可疑病灶组织进行活检。当前已发展至第二代的 SpyGlass 系统，在镜体直径设计、照明亮度以及图像分辨率等方面均有显著提升，整体临床操作性能与诊断效能均获得显著增强。SpyGlass 视觉印象诊断恶性肿瘤的灵敏度和特异度分别为 90% (95%置信区间[confidence interval, CI]，69.9%~97.2%)和 95.8% (95% CI, 79.8%~99.3%)，SpyGlass 引导活检的灵敏度和特异度为 85% (95% CI, 64.0%~94.8%)和 100% (95% CI, 86.2%~100%) [28]。一项系统综述[29]分析了 539 例患者胆道镜直视下活检的诊断效能，结果显示其灵敏度为 72%。Sun 等[30]开展的一项 Meta 分析进一步证实，单人操作胆道镜在不明原因胆道狭窄诊断中的直视下视觉判断敏感性为 90%，特异性为 87%；而使用 Spybite 活检钳进行组织取样的敏感性和特异性则分别为 69%和 98%。

2.2.2. 国产 EyeMAX 系统

EyeMAX 胆胰成像系统是由南京大学医学院附属鼓楼医院消化内镜中心与南微医学科技股份有限公司联合研发的一种新型国产经口胆道直视子镜。近期一项前瞻性研究[31]比较了新型国产 11-Fr 数字胆道镜 eyeMAX 与传统 SpyGlass 胆道镜在不明原因胆道狭窄诊断中的应用价值。研究纳入 97 例患者，其中 eyeMAX 组 50 例，SpyGlass 组 47 例。结果显示，eyeMAX 系统凭借更大的工作通道及活检钳尺寸，首次组织取样成功率明显优于 SpyGlass (92% vs. 61.7%, P = 0.001)，组织标本体积也显著更大(2.96 ± 0.69 mm^2 vs. 1.80 ± 1.61 mm^2)。在诊断效能方面，eyeMAX 直视下视觉诊断恶性病变的敏感性(91.3% vs. 66.7%)与诊断准确性(96.0% vs. 80.9%)均显著高于 SpyGlass，而组织病理诊断准确性亦有所提升(93.5% vs. 89.3%)，且未增加并发症发生率。

2.3. EUS-FNA/B 的精准穿刺

亚太地区胆道狭窄内镜活检共识[32]指出：在 ERCP 引导下组织活检未能明确诊断胆道恶性狭窄时，采用 EUS-FNA/B 有助于提高诊断效率。自 2000 年首个前瞻性病例系列研究首次报道了 EUS-FNA/B 在肝门部胆管病变诊断中的应用以来，多项回顾性研究进一步证实了该技术对 HCCA 的诊断敏感性约为 77%~89%，准确性约为 79%~91%。EUS-FNA/B 诊断恶性胆管狭窄的合并敏感性和特异性分别为 80% (95% 置信区间[CI]，74%~86%)和 97% (95% CI, 94%~99%)。一项荟萃分析显示，EUS-FNA/B 诊断肝门部胆管恶性狭窄的敏感性为 76% (95% CI, 66%~85%)，特异性为 100% (95% CI: 95%~100%)，且并发症发生率较低[33]。Fritscher-Ravens 等[34]在一项纳入 44 例 ERCP 刷检阴性患者的研究中报告，EUS-FNA/B 的灵敏度、特异度和准确率分别为 89%、100%和 91%。Eloubeidi 等[35]对 28 例胆管狭窄患者(其中 11 例为近端病变)进行研究，诊断灵敏度、特异度和准确率分别为 86%、100%和 88%。而在更大规模的 Meta 分析[33]中，EUS-FNA/B 诊断肝门部恶性狭窄的合并灵敏度为 76% (95% CI: 66%~85%)，特异度为 100% (95% CI: 95%~100%)。Onoyama 等[36]对 73 例肝外胆管狭窄患者(其中 27 例为肝门部病变)开展的研究显示，EUS-FNA/B 与 ERCP 在诊断效能方面相当，二者的敏感性分别为 81.8%和 76.0%，准确率分别为 84.2%和 88.9%，差异无统计学意义。尽管 EUS-FNA/B 诊断率高，但存在肿瘤种植转移的风险，目前文献中有 3 例相关报道，在具备潜在手术可能或计划行肝移植的患者中，应权衡 EUS-FNA/B 的诊断价值与其理论风险，避免对原发肿瘤进行穿刺[37]。

2.4. FISH 技术的分子诊断价值

荧光原位杂交 FISH 技术通过识别第 3、7、17 号染色体的多倍体改变及 9p21 位点的缺失，已被广泛应用于临床，用于判别胰胆管区域病变的良恶性质。Liew 等[38]的研究指出，FISH 在判别胆管狭窄性质方面具有较高的诊断准确性，敏感性达到 69.2%，而特异性为 82.4%。此外，Hiep 等[39]进一步证实，在胆管刷检基础上联合使用 FISH，能够明显提升胆管癌的细胞学检测率，其总体敏感性从 44.7%上升至 56.8%。此外，Kipp 等[40]的研究比较了常规细胞学检查与 FISH 在检测恶性胆管狭窄方面的效果，发现 FISH 的敏感性为 34%，高于常规细胞学检查的 15%，而特异性均为 100%。这表明 FISH 在提高胆管恶性狭窄诊断的敏感性方面具有优势。

3. 治疗策略优化

3.1. 胆道引流的个体化选择

对于有手术指征的 HCCA 患者，胆道引流被认为是优化手术条件、降低围手术期风险的关键环节，尤其适用于合并高胆红素血症、胆管炎、营养不良、拟行新辅助治疗或大范围肝切除的患者[41]-[44]。对

于无法切除的 HCCA 患者，大多数需要接受姑息性胆道引流来降低胆系压力、改善肝功能和控制反复发作的胆管炎[3]。目前，常用的胆道引流方式主要包括三类：经皮经肝胆道引流(percutaneous transhepatic biliary drainage, PTBD)、内镜下鼻胆管引流(endoscopic nasobiliary drainage, ENBD)以及内镜逆行胆道引流(endoscopic retrograde biliary drainage, ERBD)。三者各有优劣，尚无统一推荐路径。PTBD 操作简便，减轻黄疸效果好，但存在肿瘤种植转移风险。ENBD 减轻黄疸效果与 PTBD 相当，但技术要求高，有诱发胰腺炎的风险。ERBD 为内引流，更符合生理状态，包括塑料支架和自膨胀金属支架。Wiggers 等[45]回顾性研究表明，在 180 例接受 ERCP 引流的患者中，32%因 ERCP 失败转行 PTBD，且 Bismuth-Corlette IV 型是 ERCP 引流失败的主要预测因素。Kloek 等[46]研究发现，PTBD 成功率高于 ERCP (85% vs. 71%)，在胆红素下降速度方面也更具优势，两者并发症发生率相当。Sawas 等[47]的 Meta 分析显示自膨胀金属支架在支架通畅时间(平均延长约 3.5 个月)、技术成功率和减少再干预方面均显著优于塑料支架。在选择具体的胆道引流策略时，需要结合多方面因素进行个体化评估，包括梗阻所在的解剖位置、引流治疗的核心目标、医疗机构的设备条件与技术水平、术者的操作熟练程度，以及患者的全身状况和自身意愿等，综合权衡后制定最适宜的方案。如需同时行组织活检或刷检首选 ERCP，而对于 Bismuth-Corlette IV 型等复杂患者，可首选 PTBD。对于术前胆道引流或预计总体生存期(overall survival, OS) < 3 个月的 HCCA 患者，可首选塑料支架，而预计 OS > 3 个月的患者，对左肝管扩张且传统引流不充分的恶性不可切除胆道梗阻患者，超声内镜引导下胆道引流术(endoscopic ultrasound-guided biliary drainage, EUS-BD)联合肝胃吻合术是一种有效的替代方案[48]。

3.2. 腔内治疗的联合应用

当前常用于胆道内腔治疗的手段主要包括射频消融(radiofrequency ablation, RFA)、光动力疗法(photodynamic therapy, PDT)以及腔内近距离放射治疗(intraluminal brachytherapy, ILBT)等多种方式。其中，RFA 通过高频电流在靶组织内引发局部热效应，促使细胞内外水分蒸发、蛋白变性并最终引起组织坏死，从而达到局部消融肿瘤的作用。该技术多用于无法实施根治性手术的肝门部胆管癌患者，作为一种姑息性治疗手段[49]。研究表明，与单纯胆道支架引流相比，RFA 联合支架置入能显著延长患者的 OS 和改善生活质量[50]。两项小样本研究进一步证实，RFA 联合胆道支架置入在不增加不良事件发生率的同时，可显著延长患者的 OS 及支架通畅时间[51] [52]。此外，RFA 与全身化疗联合应用能够进一步提升不可切除 HCCA 患者的治疗效果，改善其长期生存预后[53] [54]。PDT 是一种利用光敏剂选择性聚集于肿瘤细胞内，在特定波长激光照射下产生光毒效应，从而诱导肿瘤细胞凋亡的局部微创治疗技术[55]。一项发表于 2022 年的 Meta 分析研究[56]显示，将 PDT 与胆道支架置入联合应用，可在不显著增加不良反应风险的前提下，延长肝门部胆管癌患者的 OS，同时显著提高支架的通畅持续时间。另有多项研究[57]-[59]指出，PDT 与化疗联合使用时展现出良好的协同效应，临床上通常采用先行 PDT 治疗、随后实施序贯化疗的综合治疗策略。由于 PDT 具有良好的重复性，推荐治疗间隔通常约为 3 个月。ILBT 作为一种局部放疗手段，其辐射作用范围有限，且具有较长的半衰期，能够对肿瘤组织产生持续性杀伤，同时对周围健康组织的影响相对较小[60]。一项涵盖 981 例恶性胆道梗阻患者的 Meta 分析[61]结果显示，与单纯置入胆道支架相比，联合应用 ILBT 可显著降低支架再阻塞的发生风险，并有效延长患者的总体生存时间，同时未观察到并发症发生率的明显上升。但 ILBT 技术本身较为复杂，放射性物质管理要求严格，且可能引发如十二指肠狭窄、胃肠道出血、胆道出血等迟发性不良事件，限制了其在临床中的广泛应用。近年来，将胆道支架置入联合碘-125 粒子植入作为 ILBT 的新兴应用方案，已有研究表明该技术能够有效延长支架通畅期并改善患者生存预后，具有良好的临床应用前景[62]。

4. 先进技术对 HCCA 诊治的影响

4.1. 人工智能技术

近年来，人工智能(artificial intelligence, AI)技术在肿瘤诊疗领域的应用日益广泛，尤其在临床决策支持与病理影像辅助诊断方面表现出巨大潜力。Ratti 等[63]构建了一种基于机器学习的模型，通过整合临床、影像及实验室参数，用于预测 HCCA 患者接受根治性手术的可能获益，有效提升了术前评估的准确性与个体化治疗策略的制定效率。该模型的引入，有望优化治疗分配，避免不必要的手术干预。此外，Kiani 等[64]开发了一种基于深度学习的数字病理辅助系统，用于辅助区分肝细胞癌与胆管癌。该系统在内部验证集和独立测试集中的诊断准确率分别为 88.5%和 84.2%，对中等经验水平的病理医生尤为显著地提高了诊断准确性。然而研究亦提示，当 AI 判断错误时，可能对诊断产生负面影响，强调在临床应用中需谨慎评估 AI 工具的可靠性，并保持医生的独立判断能力。

4.2. 影像导航技术

影像导航技术通过实时构建或融合三维影像信息，为内镜或外科操作提供更精确的可视化引导，已逐步应用于 HCCA 的术前规划与术中操作中。Zhang 等[65]在一项病例研究中将增强现实(augmented reality, AR)技术引入开腹肝门部胆管癌切除术中，结合术前影像重建，实现术中实时三维解剖导航，显著提高了手术操作的安全性与完整性。Tang [66]等进一步提出了一种结合三维/二维图像配准与呼吸运动补偿的连续图像引导系统，用于优化 ERCP 操作的实时影像引导效果。该系统可有效减轻患者呼吸带来的图像偏移，提高了 ERCP 过程中病变识别与导管置入的精准性，提升了对肝门部胆道病变的整体诊断效率。

4.3. 纳米靶向技术

纳米技术在肿瘤治疗中的靶向递药优势近年来逐步显现。其通过纳米载体将药物高效递送至肿瘤微环境，在提高局部药物浓度的同时显著降低了对正常组织的毒副作用。在胆管癌治疗方面，Ning 等[67]开发了一种基于空心二氧化锰纳米颗粒(hollow MnO_2 nanoparticles)构建的 Lenvatinib 靶向递送系统(Lenvatinib@H-MnO_2-FA)。该系统通过叶酸介导的主动靶向机制，实现 Lenvatinib 在胆管癌细胞内的高效累积，并通过激活 Raf/MEK/ERK 信号通路诱导肿瘤细胞凋亡，从而增强其抗肿瘤效能。尽管该研究目前主要聚焦于肝内胆管癌，但其所提出的纳米递药策略为 HCCA 等不可手术切除病例提供了新的治疗思路，具有良好的研究前景和临床转化潜力。

5. 总结与展望

总之，近年来，内镜技术的快速发展为 HCCA 的精准诊断与综合治疗提供了有力支持。从传统的 ERCP 联合 IDUS，到高分辨率的数字胆道镜与国产新型内镜，再到 EUS-FNA、FISH 等分子诊断技术，HCCA 的诊断手段不断优化，组织获取质量和诊断效率明显提高。在治疗方面，胆道引流方式日趋个体化，腔内治疗手段如射频消融、光动力治疗、近距离放疗等也逐步成为姑息治疗的重要补充。未来，随着人工智能、影像导航、纳米靶向等前沿技术的引入，HCCA 的内镜诊疗模式有望实现更加精准、微创和个体化的发展。

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