

壶腹部肿瘤诊疗研究进展

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摘要

壶腹癌是起源于Vater壶腹区域的恶性肿瘤, 虽整体发病率较低, 但近年呈上升趋势。因其特殊的解剖位置及复杂的生物学行为, 临床常面临早期诊断困难、手术方式选择复杂等问题。随着影像技术的持续革新、病理分型的不断细化以及治疗手段的逐步优化, 壶腹癌诊疗正从经验主导转向多维度精准评估, 以制定更具针对性的诊疗策略。本文结合该领域最新研究进展, 对壶腹癌在诊断策略、治疗选择及新兴疗法等方面的研究现状进行综述。

关键词

壶腹癌, 病理分型, 治疗策略, 研究进展, 肿瘤分期, 综述

Research Advances in Diagnosis and Treatment of Ampullary Tumors

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Abstract

Ampullary cancer is a malignant tumor originating from the ampulla of Vater region. Despite its low overall incidence, it has shown an upward trend in recent years. Due to its unique anatomical location and complex biological behavior, clinical practice often faces challenges such as difficulties in early diagnosis and complexity in selecting surgical approaches. With the continuous innovation of imaging technologies, the refinement of pathological classification, and the gradual optimization of

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treatment modalities, the diagnosis and treatment of ampullary cancer are shifting from experience-driven to multidimensional precision assessment, aiming to develop more tailored diagnostic and therapeutic strategies. This article, incorporating the latest research advances in the field, systematically reviews the current research status of ampullary cancer in terms of diagnostic strategies, treatment options, and emerging therapies.

Keywords

Ampullary Carcinoma, Pathologic Classification, Therapeutic Strategies, Research Progress, Neoplasm Staging, Review

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1. 引言

壶腹部肿瘤是一类相对罕见的恶性肿瘤，在胃肠道肿瘤中占比仅 0.2% [1]。该肿瘤源于 Vater 壶腹，即胆总管与胰管汇合处及其周围十二指肠黏膜。相较于其他壶腹周围恶性肿瘤，壶腹癌(Ampullary Carcinoma, AC)患者病程早期更易出现临床症状，这使其手术切除率远高于同类，且总体存活率亦高于胰腺癌或远端胆管癌患者[2][3]。然而，仍有相当数量的患者早期症状并不典型，这导致难以明确诊断，进而延误病情，对预后产生不利影响。此外，研究显示近 30 年来 AC 发病率呈上升趋势，年增长率达 0.63% [4]，对公共健康构成越来越大的威胁。但目前针对 AC 的相关研究依旧不足，在指导临床诊疗方面存在较大局限性。基于此，本文对 AC 的诊疗策略进行综述，以期为临床实践提供有益参考。

2. 组织学分型及免疫分子特征

壶腹的组织起源包括肠黏膜和胰胆管黏膜。AC 以腺癌常见，根据组织起源、病理形态及免疫表型特征，可分为胰胆管型(Pancreatobiliary type, PB)、肠型(Intestinal type, INT)和混合型(Mixed type, MIX)三种组织学亚型[5]。一项纳入 547 例 AC 患者的多中心回顾性研究显示，PB 占比最高(53.6%, 293/547)，INT 次之(38.6%, 211/547)，MIX 仅 43 例[6]。在排除 MIX 的相关研究中，也均证实 PB 的发生率显著高于 INT [7][8]。由于 MIX 兼具 INT 与 PB 的中间组织学及免疫表型特征，其分类常存在界定模糊。因此，多数研究将 AC 组织亚型简化分为 INT 和 PB 两种。值得注意的是，组织学分型具有重要的临床预后价值[9]。PB 往往预后不佳[1][10]-[12]，且侵袭性更强[13]。Robert 等[10]对 319 例 AC 切除患者的研究显示，INT 患者中位无病生存期长达 58.9 个月，显著优于 PB 患者的 25.3 个月($P = 0.0123$)。Kim 等[11]的研究也得出相似结论。另一项纳入 966 例患者的单中心回顾性研究显示，根治性术后 PB 中位生存期仅 23 个月，INT 患者达 71 个月[12]，提示 PB 更强的侵袭性生物学行为。现有证据显示，MIX 平均总生存期介于 PB 和 INT 之间[5][14]，但病例数有限，其预后独立影响需多中心大样本研究验证。此外，免疫组化技术通过检测特异性分子标记物，为 AC 精准分型提供客观依据。INT 主要表达 CDX2、MUC2 和 CK20；PB 常呈现 MUC1、MUC5AC 和 CK7 阳性染色，与胰腺癌、胆管癌免疫表型相似[15][16]。国内学者提出联合检测 MUC1、MUC2、CK7、CK20 及 CDX2 的表达模式，可有效鉴别包括 MIX 在内的各组织学亚型[17]。分子特征能够弥补组织学分型的局限性，其不仅用于预测预后，还能为临床制定化疗、靶向及免疫治疗方案提供依据。基于此，美国国家综合癌症网络(National Comprehensive Cancer Network Guidelines, NCCN)

指南建议, 所有确诊的 AC 患者均需常规行错配修复基因(MLH1, MSH2, MSH6, PMS2)及微卫星不稳定性(MSI)检测; 对于转移性/不可切除患者, 推荐行二代测序, 涵盖 TP53、BRCA1、BRCA2、CDKN2A 等基因, 为治疗提供依据[18]。

3. 诊断策略

3.1. 临床表现与实验室检查

AC 患者多以黄疸、腹痛、陶土色大便等非特异性症状起病, 提示恶性梗阻可能[19]。其病理基础为壶腹区域肿瘤阻塞胆汁排泄通路并引发局部组织浸润。由于上述临床表现与肝外胆管癌、胰腺癌存在显著重叠, 临床鉴别诊断常存在难度。实验室检测可见 AC 患者肝功能指标异常, 表现为血清胆红素水平升高及肝酶谱紊乱。值得注意的是, 血清 CA19-9、CA12-5 等肿瘤标志物水平常呈升高趋势, 对 AC 的辅助诊断具有参考价值[20]。

3.2. 影像学检查

3.2.1. 计算机断层扫描与磁共振成像评估

计算机断层扫描(Computed Tomography, CT)与磁共振成像(Magnetic Resonance Imaging, MRI)在显示肿瘤形态及评估侵犯范围上各有优势。CT 平扫多表现为胰头下方十二指肠降部内壁的结节状肿块, 增强扫描可见动脉期显著强化[21]; 而 MRI 常呈现不均匀强化的肿块或强化的增厚导管壁, 可清晰显示胆总管与胰管扩张、胆总管偏心性不规则狭窄及壶腹部充盈缺损[22]。其扩散加权成像表现为高信号, 能进一步提高 AC 诊断的敏感性和特异性[23]。尽管部分研究显示 MRI 对 AC 的诊断准确率高于 CT [24] [25], 但 CT 在评估肿瘤对相邻器官侵犯的灵敏度上更具优势[26]。且 CT 平扫胸腹部及骨盆是 AC 临床分期的基础手段[27] [28]。柴瑾等[29]在一项基于肿瘤病理亚型的 CT、MRI 影像学差异研究表明, INT 以腔内生长为主, 边界清晰、密度/信号均匀, 且肿瘤位置更靠近十二指肠乳头; 而 PB 腔内型与腔外型生长比例相近, 边界模糊、密度/信号不均, 较 INT 更易侵犯胰腺组织, 显示出更强的侵袭性。多排计算机断层扫描作为 CT 的进阶技术, 在评估胆道扩张程度、病变特征、周围组织侵犯及增强模式方面优势显著[30]; 与此同时, 磁共振胰胆管成像对低位胆道梗阻性病变的诊断与鉴别具有重要意义[20]。此外, 2-[¹⁸F]氟代脱氧葡萄糖正电子发射断层显像/X 线计算机断层成像(2-[¹⁸F]Fluoro-2-deoxy-D-glucose Positron Emission Tomography/Computed Tomography, ¹⁸F-FDG PET/CT)作为功能成像技术, 可通过检测肿瘤糖酵解活性, 弥补 CT、MRI 等传统解剖影像学在壶腹癌淋巴结微转移、隐匿性远处转移评估中的不足, 进一步完善肿瘤术前分期的准确性。其对 AC 淋巴结转移的检测特异性达 95.3%、阳性预测值 92.7%, N 分期敏感性(54.3%)显著优于 MRI (25.0%), 远处转移检测的特异性及阳性预测值均为 100%, 可有效排除 M1 期患者[31]。该技术与 CT、MRI 联合可实现解剖形态与代谢活性的双重评估, 尤其对内镜乳头切除术(Endoscopic Papillectomy, EP)候选者, 能识别 10%的隐匿性恶性或淋巴结转移病例, 优化术式选择决策[31]。

3.2.2. 超声检查

超声检查凭借操作简便、可重复扫描的优势, 对肝内外胆管扩张具有高度敏感性[20]。通过调整体位及使用高频传感器, 可改善肝外胆管的可视化效果, 但受限于胃肠道气体干扰及复杂解剖结构, 对肝外胆管及 Vater 乳头病变的检出存在困难[32]。尽管超声对 AC 的检出率不足 30% [33], 且敏感性低于 CT [20] [24] [25], 但对肝门部癌及胆囊癌的肿瘤显示能力较强, 在鉴别诊断中具有重要的辅助价值[32]。值得注意的是, 作为侵入性成像技术, 胆管内超声可提供胰胆管及邻近结构的实时横断面高清图像, 被证

实是评估 AC 敏感性高且具有独特价值的工具[34]。

3.2.3. 内镜检查与超声内镜技术

对于诊断困难的壶腹区域病变, 可通过食管胃十二指肠镜检查并获取活检, 以明确病理诊断[18]。由于壶腹部占位通常体积较小, 临床诊断存在一定难度, 内镜活检的准确性差异较大[35]。超声内镜 (Endoscopic Ultrasonography, EUS) 作为内镜与超声结合的微创技术, 可在内镜直视十二指肠乳头区域的同时, 通过超声探头实时扫描病变, 对可疑病灶行细针穿刺活检, 明确病变起源与病理性质。尽管 EUS 在评估淋巴结转移方面存在一定局限性[36], 但肿瘤越小, EUS 的诊断优势越显著, 对术前分期具有重要的指导意义, 能弥补常规超声及内镜的诊断不足[36]-[38]。此外, 其使许多患者避免了因不必要的内镜逆行胰胆管造影术操作而导致的潜在并发症[39]。作为 EUS 技术的重要改良, 造影增强超声内镜技术通过实时显示肿瘤血流灌注特征, 有望进一步提升壶腹肿瘤的检出率[40]。

4. 肿瘤分期

AC 的分期可参考美国癌症联合委员会 (American Joint Committee on Cancer, AJCC) 第 8 版分期系统 (表 1), 其 T 分期标准基于肿瘤侵犯范围精准界定如下: 肿瘤局限 Oddi 括约肌或壶腹部为 T1a, 肿瘤侵犯超出 Oddi 括约肌范围或十二指肠粘膜下层为 T1b; 当侵犯到十二指肠固有肌层为 T2; T3 包括 T3a (侵犯胰腺深度 ≤ 0.5 cm) 和 T3b (侵犯胰腺深度 > 0.5 cm 或侵犯十二指肠浆膜下/胰腺周围软组织); T4 定义为侵及腹腔动脉干、肠系膜上动脉和/或肝总动脉的肿瘤[41]。

Table 1. AJCC eighth edition AC staging system

表 1. AJCC 第八版 AC 分期方案

T	N	M
Tx: 原发性肿瘤无法评估	Nx: 无法评估淋巴结	Mx: 不能评估远处转移
T0: 无原发性肿瘤证据	N0: 无淋巴结受累	M0: 没有远处转移
T1a: 限于 Oddi 括约肌或 vater 壶腹	N1: 1~3 个淋巴结转移	M1: 远处转移
T1b: 侵犯超出 Oddi 括约肌和/或十二指肠粘膜下层		
T2: 侵及十二指肠固有肌层	N2: 4 个或更多淋巴结转移	-
T3a: 侵犯胰腺 ≤ 0.5 cm	-	-
T3b: 侵犯胰腺 > 0.5 cm 或侵犯十二指肠浆膜下/胰腺周围软组织		
T4: 累及腹腔动脉, 肠系膜上动脉, 和/或肝总动脉	-	-

5. 治疗

5.1. 胆道减压

AC 大多数患者常出现黄疸, 严重胆道梗阻影响患者围术期安全[42]。因此, 对于该类患者, 可行术前胆道减压[18]。胆道减压包括经皮胆道引流 (Percutaneous Transhepatic Biliary Drainage, PTBD) 和内镜逆行胆道引流 (Endoscopic Retrograde Biliary Drainage, ERBD), 但目前关于术前胆道引流方式尚未达成共识 [43] [44]。未来需更多大样本量、多中心研究比较两种方式对 AC 患者术后生存及长期预后的影响差异, 以进一步优化术前胆道减压策略。总之, AC 术前胆道减压需在充分评估患者病情、技术可行性及并发症风险的基础上, 遵循“个体化、安全优先”原则, 合理选择 PTBD 或 ERBD, 最终目标是改善围术期安全、为根治性手术创造条件。

5.2. 核心切除手术方式及对比

切除 AC 的主要治疗方式是胰十二指肠切除术(Pancreaticoduodenectomy, PD)、经十二指肠壶腹切除术(Transduodenal Ampullectomy, TDA)和 EP [45], 三种术式的适应症、临床疗效及安全性各有差异, 现集中对比阐述如下。

5.2.1. 经十二指肠壶腹切除术

TDA 的适应症包括 Tis 癌、显示胆管或胰管进展 >20 mm 的腺瘤, 因憩室或肿瘤直径 ≥ 40 mm, 导致 EP 存在技术困难的大腺瘤[46]。对于无法接受 EP 或 PD 的壶腹肿瘤患者, TDA 这是一种可供选择的治疗方法。研究显示[47] [48], TDA 的围术期并发症发生率与死亡率均处于临床可接受范围, 并且随着微创技术的发展, 腹腔镜经十二指肠壶腹切除术(Laparoscopic Transduodenal Ampullectomy, LTDA)具有住院时间短、失血量少的优势[49]。与 PD 相比, TDA 的围术期并发症发生率与死亡率更低, 但由于有限的组织切除和淋巴结清扫, 复发率较高[50]。与 EP 相比, 两组在不良事件发生率上无显著差异, EP 组住院时间更短、侵入性更低[46]。但 EP 复发率较高[45]。因此, TDA 是治疗壶腹肿瘤的一种可行且有效的术式, 但仅适用于严格筛选的患者。

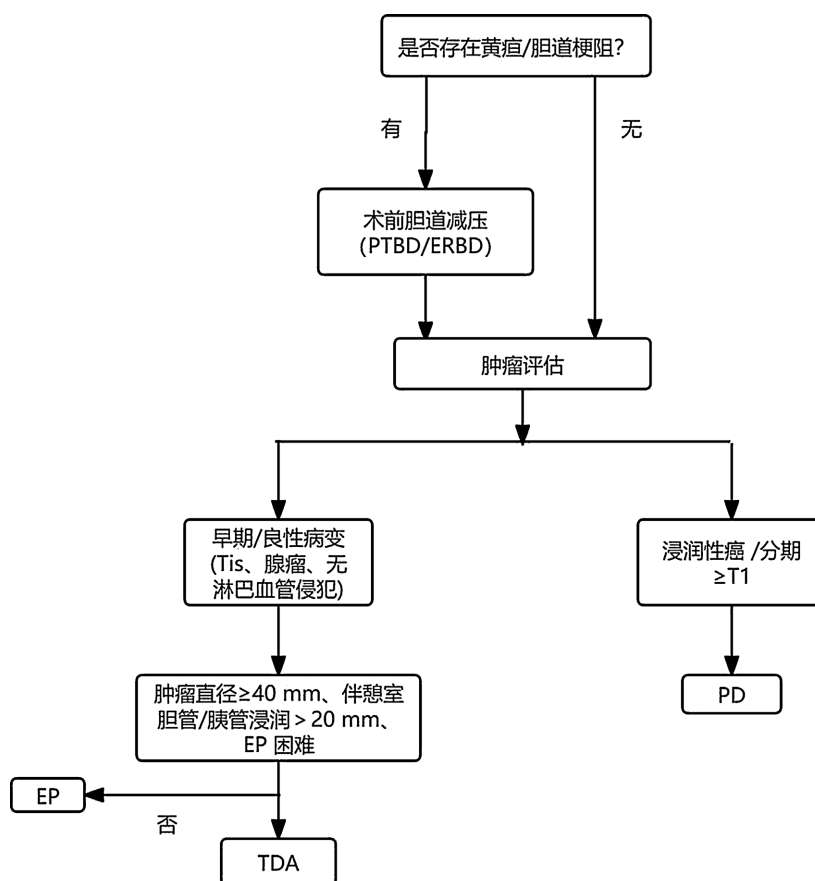
5.2.2. 胰十二指肠切除术

PD 是 AC 的首选治疗方式, 其核心优势在于通过系统性淋巴结清扫联合肿瘤整块切除实现治愈性疗效[1] [50]。尽管 PD 术后并发症发生率较高, 但 AC 患者的长期生存预后显著优于胰腺癌[2], 且外科手术治疗可带来明确的生存获益[51]。荟萃分析显示, 与 EP 相比, 手术切除在实现肿瘤 R0 切除方面具有显著优势[52]。淋巴结转移状态是 AC 总生存期的独立预后因素[1] [53], 因此清扫足够数量的淋巴结至关重要[54]。即使临床分期为 T1 期的早期 AC, 淋巴结转移率仍可达 10%左右[50] [55], 而肠系膜血管周围淋巴结是最常见的复发部位[55], 这提示根治性手术对阻断转移路径的必要性。Hong 等[50]及 Lai 等[56]的研究显示, 尽管 TDA 与根治术组在 5 年无病生存率和总生存率上无统计学差异, 但根治术组纳入的病例多为更具侵袭性的肿瘤, 表明根治术对进展期病变的必要性。与传统 PD 相比, 腹腔镜胰十二指肠切除术(Laparoscopic Pancreaticoduodenectomy, LPD)在无复发生存期和总生存率上无显著差异, 但具有术后疼痛轻、并发症率低及住院时间缩短等优势[54]。机器人胰十二指肠切除术(Robotic Pancreaticoduodenectomy, RPD)虽具备相似疗效, 但其高昂费用限制了广泛应用[57]。随着加速康复外科(Enhanced Recovery After Surgery, ERAS)理念的深入, 即使是老年患者术后也能获得良好预后[58]。因此, PD 联合规范淋巴结清扫仍是 AC 获得长期生存的核心手段, 随着微创技术和 ERAS 理念的普及, 该术式的安全性和耐受性显著提升, 使更多患者从中获益。

5.2.3. 内镜下切除

EP 是通过内镜下切除十二指肠黏膜及黏膜下层, 完整移除 Vater 壶腹及其周围胆管、胰管开口区域的病变组织[59]。操作主要借助内窥镜圈套器, 配合电外科纯切割电流或混合电流完成, 是特定壶腹病变的有效治疗手段, 为传统外科手术提供了微创化替代方案[60]。近年来, EP 不仅用于良性病变, 还用于早期 AC, 其定义为局限 Oddi 括约肌内且无淋巴、血管侵犯的 AC 患者[61] [62]。Hwang 等[63]回顾性分析了接受单独 EP 或 EP 后 PD 的早期 AC 患者。尽管他们发现所有早期患者淋巴血管侵犯率为 5.7%, 但两组肿瘤复发率没有统计学显著差异, 因此严格筛选适应症是 EP 安全应用的前提。一项纳入 29 项研究共 1751 例 AC 患者的荟萃分析显示, 内镜下完全切除率达 94.2%, 治愈性切除率为 87.1% [64]。对比 TDA, EP 复发率较高[45], 复发率为 11.8% [64]。此外, 家族性腺瘤性息肉病患者即使实现完全切除, 仍因潜在遗传背景面临更高的复发风险[65]。Heise 等[45]的荟萃分析证实, EP 的并发症风险显著低于 PD

及 TDA。总体不良事件发生率为 24.9%，以术后胰腺炎(11.9%)和出血(10.6%)最常见，其次为穿孔和胆管炎，长期并发症(如乳头狭窄)仅 2.4% [64]。内镜黏膜下注射(生理盐水、亚甲蓝或肾上腺素)的作用尚不明确，Hyun 等[66]的前瞻性多中心研究显示，其对完全切除率的提升无显著优势，与单纯圈套切除术相当。可能因壶腹区解剖复杂导致效果受限。氩等离子体凝固、光动力疗法、单极和双极凝固、导管内射频消融和钕-钇铝石榴石激光等内镜下消融技术可作为肿瘤姑息性治疗方法[67]。与未接受辅助治疗的患者相比，辅助热消融治疗的成功率相似[68]，此类辅助治疗的临床获益仍存在争议。综上，AC 手术治疗的选择需以肿瘤大小、浸润深度、淋巴结转移状态及患者全身手术耐受度为核心评估依据综合判定，上述诊疗决策通过 AC 治疗决策(图 1)梳理呈现。



注：PTBD：经皮胆道引流；ERBD：内镜逆行胆道引流；PD：胰十二指肠切除术；TDA：经十二指肠壶腹切除术；EP：内镜乳头切除术。

Figure 1. Surgical treatment decision flowchart for ampulla cancer
图 1. 壶腹癌手术治疗决策流程图

5.3. 辅助治疗

目前，围绕 AC 术后辅助治疗的临床获益仍存在争议，尽管大多数中心以辅助化疗联合放疗为标准方案[69]，但其获益仍需更精准的人群分层。Nassour 等[70]对 4190 例 AC 患者的分析显示，辅助放化疗与生存率提高相关，辅助放化疗组的中位总生存期为 47.2 个月，而观察组为 31.0 个月，尤其在高危患者中获益更为显著。Ha 等[71]、Jin 等[72]的研究也得出类似结论。然而，部分研究指出，辅助放化疗并未显著改善 AC 患者的生存获益[69] [73]，这可能源于 AC 的强异质性，如肠型、胰胆管型，不同组织学分

型对治疗的反应存在差异。基于此, 目前临床可参考 NCCN 指南建议, 所有阶段的 AC 均可接受全身治疗, 术后应常规行病理检测及亚型分型, 以指导个体化辅助治疗, 从而降低复发风险并延长总生存期; 对于转移性患者, 需通过多基因检测实现分子分型, 以探索靶向治疗及免疫治疗等精准医疗手段[18]。

6. 总结与展望

AC 作为一种罕见但发病率呈上升趋势的恶性肿瘤, 其早期症状隐匿、病理亚型复杂, 对临床诊断和治疗提出了严峻挑战。当前, 早诊早治仍是改善预后的关键策略。通过内镜检查、多模态影像学、肿瘤标志物及免疫组化分子分型的综合应用, 可实现诊断、分期与病理评估, 为个体化治疗提供依据。早期 AC, EP 是优选方式, 若 EP 存在技术操作困难, 可选择 TDA。而 PD 仍是根治性治疗的标准术式, 通过系统性淋巴结清扫和无瘤切缘提升长期生存, 联合 ERAS 理念可有助于降低术后并发症, 改善围术期安全性。术后需基于组织学分型制定个体化辅助治疗方案以减少复发。在未来, 针对病理亚型的异质性, 需开展大样本、前瞻性研究, 探索基于分子特征的精准诊疗策略, 包括靶向治疗、免疫治疗等新兴手段, 以期进一步优化治疗方案、改善患者生存质量。

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