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·述评·

胆囊癌外科治疗中的难点、争议与思考

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摘　要　胆囊癌是胆道系统中最常见的恶性肿瘤，具有隐匿生长、快速进展和跳跃性转移的特点，5年总体生存率仅5%。近年来的靶向和免疫治疗虽不断涌现，但在胆囊癌的治疗中仍处于探索阶段，根治性手术切除仍是目前唯一可能治愈胆囊癌的方法。手术的主要目标是完全切除肿瘤病灶，并进行系统的淋巴结清扫，以降低复发的风险。得益于手术技术的进步和围手术期管理的不断优化，接受扩大胆囊癌根治术患者的术后并发症和住院病死率有所下降。然而，胆囊癌复杂的扩散和转移机制导致确定手术切除的最佳范围十分困难。不同国家的临床指南和各肝胆外科中心在手术方案的选择上意见并不一致，尤其是在肝切除的合理范围、淋巴结清扫的范围及其对预后的影响，以及是否应常规进行肝外胆管切除等方面，存在较多争议。未来仍需要开展大型前瞻性队列研究来为胆囊癌的外科治疗提供更多的循证医学证据。当前，在制定手术方案时，外科医生需要综合考虑患者术前检查结果、术中所见以及冷冻切片的病理评估，在根治与安全和有效之间寻求平衡，选择最适合患者的手术方式，同时重视多学科协作体系的建设，根据肿瘤的准确分期，在术后结合有效辅助治疗，方能在改善患者的预后方面继续取得进展。

关键词　胆囊肿瘤；肝切除术；淋巴结切除术；肝外胆管切除术
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Challenges, controversies, and considerations in the surgical treatment of gallbladder cancer

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Abstract　Gallbladder cancer is the most common malignant tumor of the biliary system, characterized by insidious growth, rapid progression, and skip metastasis. The 5-year overall survival rate is only 5%. Although targeted immunotherapies have emerged in recent years, they are still in the exploratory phase for the treatment of gallbladder cancer, and radical surgical resection remains the only potentially curative

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treatment. The main goal of surgery is to completely remove the tumor and perform systematic lymph node dissection to reduce the risk of recurrence. Thanks to advances in surgical techniques and continuous optimization of perioperative management, postoperative complications, and hospital mortality in patients undergoing extended radical surgery for gallbladder cancer have decreased. However, the complex mechanisms of gallbladder cancer spread and metastasis make it challenging to determine the optimal scope of surgical resection. Clinical guidelines from different countries and hepatobiliary surgery centers often vary on surgical options, especially regarding the reasonable extent of liver resection, the scope of lymph node dissection and its impact on prognosis, and whether routine extrahepatic bile duct resection should be performed. There remains significant controversy in these areas. Future extensive prospective cohort studies are still needed to provide more evidence-based medical data for the surgical treatment of gallbladder cancer. When designing a surgical plan, surgeons must consider preoperative examination results, intraoperative findings, and pathological evaluation of frozen sections. A balance must be struck between radical treatment and safety and effectiveness. The most appropriate surgical method for each patient should be chosen while also emphasizing establishing a multidisciplinary collaborative system. Based on accurate tumor staging, postoperative adjuvant therapies should be integrated to continue making progress in improving patient prognosis.

Key words Gallbladder Neoplasms; Hepatectomy; Lymph Node Excision; Extrahepatic Bile Duct Resection

CLC number: R735.8

胆囊癌是一种高度恶性的消化系统肿瘤，预后较差，即使行胆囊癌根治术，患者5年生存率也只有10%~25%[1-3]。外科手术作为胆囊癌治疗的核心手段，其手术范围的选择和技术的优化对提高患者的生存率和生活质量具有重要影响。近年来，随着手术技术与术后管理的进步，扩大胆囊癌根治术的术后并发症和在院病死率有所下降。但由于以下三点原因，当前对于不同分期胆囊癌患者手术方式的选择仍有争议：(1) 胆囊毗邻肝脏，两者间的分界无浆膜覆盖，胆囊癌生物学行为具有隐匿生长，侵袭性强和跳跃性转移的特点，易在肝脏和淋巴结中出现转移；(2) 不同肝胆外科中心进行的临床研究观察结果不一致，导致了治疗理念的差异；(3) 目前大部分关于胆囊癌外科治疗的临床研究病例数较少，缺乏针对胆囊癌外科治疗的大规模多中心临床研究，研究结果说服力不强。本文旨在探讨胆囊癌外科治疗中的关键问题，包括肝切除范围、淋巴结清扫和肝外胆管切除的策略与要点。

1 肝切除范围与肝胰十二指肠切除术

1.1 Tis和T1期

原位癌和侵及胆囊黏膜固有层的胆囊癌多在术中或术后的病理检查发现[4]。目前国内外专家一致认为，Tis和T1a期的胆囊癌患者，在避免胆囊破裂的情况下只需要进行单纯的胆囊切除术即可实现R_0切除。胆囊和肝脏之间的边界是Glisson鞘延续而成的囊板[5]，无浆膜，侵犯肌层的胆囊癌可以沿血管和淋巴管向肝脏或远处转移，因此对于T1b期及以上的患者行扩大胆囊切除术才能够实现根治[6]。目前的主流观点支持T1b期胆囊癌施行胆囊切除术和距离胆囊床2 cm以上的肝脏楔形切除即可达到根治效果[7]。

1.2 T2期

目前认为T2期胆囊癌扩散到肝脏有多种潜在的机制。Endo等[8]通过分析20例T2期胆囊癌患者的病理切片，发现原发肿瘤内的血管浸润数目是胆囊癌发生肝转移的重要影响因素，并且肝脏侧肿瘤相较于腹腔侧肿瘤更易发生肝脏转移。据统计[9]，33%的T2b期胆囊癌患者在肿瘤邻近肝组织内发现了微转移灶。在肝脏切除的具体范围方面，目前尚没有统一的观点。祝家海等[10]纳入8项研究

进行了Meta分析发现，T2a期和T2b期的胆囊癌，无论行距胆囊床2 cm以上的肝组织切除术还是肝IVb+V段切除术，只要实现了R_0切除，患者的5年生存率没有差异。同样，日本研究者[11]纳入7项研究的Meta分析研究了楔形切除术与肝S4b+S5段切除术治疗T2和T3期胆囊癌的手术和肿瘤学结果，结果表明两种肝切除范围的肝转移、5年无病生存期和总生存期对比没有差异，因而提倡小范围的肝切除。与之相反，Chen等[12]研究结果却显示接受肝脏IVb+V段切除术的患者相较于接受楔形切除术的T2期胆囊癌患者有更高的无病生存率，这一差异在偶发性胆囊癌或T2期胆囊癌患者中更加显著。

此外，近年的研究在T2期患者接受肝组织切除术后能否获益上也存在争议。一项纳入了18项研究的Meta分析[13]表明，若术前评估表明肿瘤局限在肌周结缔组织，并且术中冷冻切片证实手术获得阴性切缘的胆囊癌患者，不需要行肝组织切除术。另一项回顾性研究[14]也支持这一结论，其结果显示，与联合淋巴结清扫的胆囊切除术相比，同时进行肝切除术的患者没有获得更好的5年无病生存率，反而有更高的术中出血量和住院时间。但是，Sung等[15]进行的包含147例T2期胆囊癌患者的回顾性研究结论相反，认为不同的手术方式对T2a期胆囊癌患者的生存率没有影响，但是在T2b期胆囊癌患者中，胆囊癌根治术的总生存率高于单纯胆囊切除术和联合淋巴结清扫的胆囊切除术。You等[16]在一项纳入118例T2期胆囊癌患者的回顾性研究中指出，通过术前影像学检查确定的T2期胆囊癌，其准确率仅为68%，接受肝组织切除术的T2a期患者的5年生存率优于仅接受胆囊切除术的患者。

由于T2期胆囊癌可在距胆囊床5 cm的肝组织中出现微转移[17-19]，加之前述术前影像对T2期胆囊癌的判断准确率不高，笔者团队出于对T2期胆囊癌患者行肝楔形切除术可能无法实现R_0切除的担忧，因而更倾向于对T2期胆囊癌患者行肝IVb+V段切除术。

1.3　T3和T4期

T3和T4期肿瘤已经穿透胆囊的浆膜并侵犯邻近脏器，预后不佳，术后1年的复发率达40%[20]，往往需要更大的手术切除范围来实现R_0切除。T3期肿瘤的肝切除范围需要根据肿瘤侵犯肝脏的程度来确定。国内指南认为，T3期胆囊癌在肝床受累<2 cm、无肝十二指肠韧带淋巴结转移的情况下，肝脏IVb+V段切除即可达到R_0切除[21]，而在胆囊癌肝床受累≥2 cm或肿瘤局限于右半肝且转移灶数目为2个或肿瘤侵犯肝右动脉或肿瘤位于胆囊管、颈，侵犯胆囊三角或合并肝十二指肠韧带淋巴结转移时则应行右半肝或右三叶切除。欧美国家指南[22]同样建议对进展期的胆囊癌需要扩大肝切除范围。但是日本指南[23]则建议对于肿瘤肝脏侵犯较为局限的患者，采用非解剖方法切除具有足够切缘的胆囊床周围肝组织优于IVb+V段切除。10%~25%接受胆囊癌根治性手术的患者需要大范围肝切除术（>3段），部分患者甚至需要切除胃、结肠、十二指肠、门静脉等邻近器官。对于伴有下段胆管受累、肿瘤浸润胰腺实质或者胰周淋巴结转移的胆囊癌，则需要施行肝胰十二指肠切除术才能达到R_0切除。名古屋大学的一项前瞻性研究[24]对比了仅接受大范围肝切除术和联合胰十二指肠切除术晚期胆囊癌患者的生存资料，发现仅接受大范围肝切除术的患者有更好的总生存期、更低的围术期并发症发生率和病死率，但是他们同时也指出联合胰十二指肠切除术的患者往往肿瘤分期更晚，由此否定肝胰十二指肠切除术对伴有局部扩散的晚期胆囊癌患者的治疗作用似乎不太妥当。随着外科技术、麻醉技术和围术期护理的不断改进，肝胰十二指肠切除术的围术期病死率在一些经验丰富的中心已经低于10%[25-26]。近年来的不少研究[25-28]认为，肝胰十二指肠切除术可以使可行根治性切除的局部扩散的晚期胆囊癌患者生存获益。但是，一项汇集了133个中心、3 676例患者的回顾性研究[29]却认为肝脏大范围切除术和联合器官切除与生存率的提高没有明显相关性，反而与更高的围术期发病率和病死率相关。虽然胆囊癌扩大根治术的安全性总体上有所改善，但由于缺乏评估更广泛手术对生存影响的前瞻性数据，它们在胆囊癌治疗中的价值尚不明确，在外科实践中，术者应综合评估患者状况后审慎开展。

2　淋巴结清扫

淋巴结转移是胆囊癌重要的转移途径，越来越多的研究表明淋巴结清扫可以改善患者的预后。Goel等[30]分析了76例T1b期患者的淋巴结转移情

况，在中位淋巴结获取数目为8枚的情况下，T1b期胆囊癌的淋巴结阳性率约为21%，在中位随访时间47.5个月后，淋巴结阴性和阳性队列的3年总生存期和无病生存期没有差异，但是淋巴结阳性组的复发率高达43%，而淋巴结阴性组仅有8.3%，因而建议胆囊癌根治术需要把门静脉周围淋巴结清扫作为标准处理。Steffen等[31]研究了SEER数据库的2 112例胆囊癌患者，虽未观察到淋巴结清扫对T1期患者的治疗作用，但在T2期患者中发现了生存获益。Kemp等[32]在对2 302例胆囊癌患者的分析中发现不进行淋巴结清扫的患者与淋巴结阳性患者的总生存期相似，进行淋巴结清扫与可切除非转移性胆囊癌患者的死亡风险降低48%相关，尤其对改善T2和T3期患者的预后十分重要。接受充分淋巴结清扫术的患者可以更好地实现R_0切除，有更准确的分期，这类患者更倾向于接受术后的辅助治疗，因而可能有更好的预后。

国内外专家一致认为Tis和T1a期胆囊癌不需要进行淋巴结清扫，T1b期及以上胆囊癌患者需要进行淋巴结清扫，并且获取淋巴结的数目至少为6枚[21, 23, 32-33]，以便于进行准确病理分期和预后评估。对于T3期胆囊癌患者，有学者甚至认为检测8枚以上淋巴结才能够进行准确分期。但是在临床实践中，接受淋巴结清扫术的患者比例并不高[34-36]。2015版和2019版指南[19, 21]都认为腹主动脉旁淋巴结是判断胆囊癌有无转移的重要标志，术中活检若为阳性，不建议行胆囊癌根治术。目前已不主张扩大淋巴结清扫，结合胆囊癌淋巴回流的特点，对于有指征胆囊癌患者的淋巴结清扫范围，笔者较为赞成以下观点[37-38]：T1b和T2期常规行淋巴结清扫，清扫范围包括肝总动脉周围（8组）淋巴结、肝十二指肠韧带（12组）淋巴结和胰十二指肠背侧上缘（13组）淋巴结；T3和T4期常规行淋巴结清扫，清扫范围包括肝总动脉周围（8组）淋巴结、腹腔动脉（9组）淋巴结、肝十二指肠韧带（12组）淋巴结、胰十二指肠背侧上缘（13组）淋巴结和肠系膜上动脉周围（16组）淋巴结。

3 肝外胆管切除

胆囊癌根治术是否需要常规开展肝外胆管切除同样颇具争议。胆囊癌根治术联合肝外胆管切除的常见适应证是肿瘤浸润肝十二指肠韧带或胆管。目前的主流观点不建议常规进行肝外胆管切除，而是术中根据胆管切缘的活检来判断是否进行肝外胆管的切除。

有研究[39-41]表明，肿瘤在胆囊中的起源位置对预后有重要的影响。累及胆囊颈和胆囊管的肿瘤更容易出现神经周围浸润，淋巴转移和非R_0切除，对此类患者行扩大胆囊切除联合肝外胆管切除有助于改善患者的预后。由于胆管周围淋巴管是胆囊癌转移的重要途径，有学者[42-44]认为，常规进行肝外胆管切除有助于更加充分地切除肿瘤病灶和进行淋巴结清扫，从而改善患者的预后。但也有不少研究[45-49]支持常规切除肝外胆管不能够增加淋巴结清扫数目或改善预后，反而增加术后并发症的发生率。Igami等[50]在52例接受胆囊癌根治术联合肝外胆管切除的无肝外胆管侵犯的患者中发现了9例患者伴有胆管周围血管、淋巴和神经的微浸润，即使接受了肝外胆管切除，这9例患者的预后仍未明显改善，没有患者的总生存期超过2年。这些结果表明胆囊癌的扩散转移机制十分复杂，未来仍需要进一步的广泛研究来验证常规肝外胆管切除的有效性。

4 小结与展望

综上所述，手术切除作为胆囊癌患者唯一可能治愈的方式，切除的关键在于完整地切除病灶并进行充分的淋巴结清扫，获取准确的分期以指导后续辅助治疗。然而根治性切除的范围达到何种程度才能够使患者获益最佳仍不清楚。胆囊癌扩散转移的复杂性导致了不同国家和地区的指南建议、不同治疗中心的理念不一。淋巴结清扫作为胆囊癌根治性切除的重要组成部分，有效完成度并不高。结合患者具体情况，以肝胆外科手术为基础开展多学科辅助治疗能够使患者获得最大生存获益。未来仍需要更大范围的临床研究确定胆囊癌根治术的最佳范围，并推动淋巴结清扫术的开展。此外，在人工智能技术迅猛发展的当下，利用人工智能图片识别技术对超声、CT和MR影像中的胆囊癌肿瘤病灶进行识别可能也有助于外科医生进行更准确的术前评估。

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