

意外胆囊癌规范化诊疗研究进展

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摘 要

意外胆囊癌(incidental gallbladder cancer, IGBC)是因胆囊良性疾病接受胆囊切除术后, 通过术中或术后病理发现的胆囊癌。由于胆囊癌常伴随胆囊结石和息肉等良性病变, 且早期缺乏特异性的临床表现和影像学特征, 导致IGBC占有胆囊癌病例的2/3以上。目前, 根治性胆囊切除术仍是其最佳治疗手段, 但针对IGBC的术前评估、手术方案选择、手术范围等仍存在不少分歧。本文系统综述了IGBC的诊疗现状、规范化治疗进展, 旨在为临床提供科学、规范的诊疗指导, 推动IGBC的早期发现与个体化治疗, 最终改善其临床结局。

关键词

意外胆囊癌, 术前评估, 根治性二次手术, 规范化诊疗

Research Advances in the Standardized Diagnosis and Treatment of Incidental Gallbladder Cancer

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Abstract

Incidental gallbladder carcinoma (IGBC) is defined as gallbladder cancer discovered incidentally through intraoperative or postoperative pathological examination following cholecystectomy performed for presumed benign gallbladder disease. Given that gallbladder carcinoma is often

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concomitant with benign conditions such as gallstones and polyps and lacks specific clinical manifestations or distinctive imaging features in its early stages, IGBC accounts for over two-thirds of all gallbladder cancer cases. Currently, radical cholecystectomy remains the optimal treatment; however, significant controversies persist regarding the preoperative evaluation, selection of surgical strategies, and the extent of resection for IGBC. This article provides a systematic review of the current diagnostic and therapeutic landscape, as well as advances in the standardized management of IGBC. It aims to offer scientific and standardized clinical guidance, promote the early detection and personalized treatment of IGBC, and ultimately improve its clinical outcomes.

Keywords

Incidental Gallbladder Cancer, Preoperative Evaluation, Radical Re-Resection, Standardized Diagnosis and Treatment

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1. 前言

胆囊癌(gallbladder carcinoma, GBC)是发病率第五的消化系统恶性肿瘤,也是最常见的胆道恶性肿瘤。由于其具有较强的侵袭性和早期淋巴结转移倾向,胆囊癌患者预后较差[1],根治性切除仍是胆囊癌患者获得长期生存的最佳手段。据统计,约有 70%的胆囊癌患者是因胆囊良性疾病(如胆囊结石、胆囊炎、胆囊息肉等)接受胆囊切除术术中或术后病理检查证实为 GBC,称为意外胆囊癌(incidental gallbladder cancer, IGBC) [2]。随着腹腔镜胆囊切除术的普及和术后病理检查的常规化,IGBC 的患者数量呈上升趋势,新近文献报道术后 IGBC 确诊率为 0.14%~1.6% [3]。IGBC 患者中大部分为 T1、T2 期胆囊癌,而早期胆囊癌缺乏典型的临床表现和影像学特征,难以在术前明确诊断,常导致治疗的延误及患者预后不良。因此,如何提高早期 GBC 的诊断率,是减少 IGBC 发生的关键。虽然 IGBC 多为早中期,组织分化程度较好,但因术前未明确诊断手术时往往未按恶性肿瘤的原则处理,易导致肿瘤细胞种植和转移,从而显著增加复发风险并影响患者的整体生存率。因此,规范化诊疗对于减少术中肿瘤细胞扩散、提高根治性切除率以及改善患者预后具有重要意义。术前诊断准确和病理分期评估是制定合理手术方案的基础,对于确定手术范围和预后评估尤为关键[4]。此外,应用荧光腹腔镜、术中高分辨率超声等先进技术,有助于识别肿瘤范围及周围组织的受侵情况,指导手术操作,提高 R0 切除率,降低肿瘤细胞的扩散风险[5]。

目前,IGBC 的诊疗尚无统一的标准,在术前评估、手术方式选择、接受根治性二次手术的最佳时机、手术切除范围及辅助治疗方案等方面存在较大争议。本文旨在系统总结近年来 IGBC 规范化诊疗方面的研究进展,推动临床实践的标准化和优化,以期减少 IGBC 的发生和促进 IGBC 患者的规范化诊疗提供帮助。

2. 胆囊良性疾病术前评估

2.1. 术前高危因素的评估

经流行病学调查研究发现,胆囊癌与胆囊黏膜受到长期慢性炎症刺激从而诱导正常的细胞发生癌变有关[6]。胆囊黏膜慢性炎症相关的疾病可提高胆囊癌的发病率,导致 IGBC 发生。有研究报道,具有胆囊结石、胆囊息肉、胆囊腺肌症及瓷化胆囊等相关危险因素的患者,其意外胆囊癌发生率可达 1.5%,是

没有任何危险因素患者发生率(0.03%)的 50 倍[7]。胆囊癌发生的其他高危因素包括：原发性硬化性胆管炎、胆胰管汇合异常、高龄女性、长期吸烟酗酒、多胎妊娠、肥胖、饮食习惯、黄曲霉素等[8]。应充分认识胆囊癌的流行病学特点以及相关危险因素，必要时可采用一定的治疗措施进行干预并定期复查，实现早期发现，早期治疗，从而避免意外胆囊癌的发生。

目前已有多种术前预测评分系统用于胆囊癌风险的量化评估。有研究通过结合术前血清癌胚抗原(CEA)和肿瘤直径等指标建立的评分系统能够有效预测 pT2 期胆囊癌，曲线下面积(AUC)达到 0.873，可较准确地预测胆囊癌的浸润深度，辅助制定手术策略[9]。基于超声、CT 及 MRI 影像学指标，联合患者的临床特征，建立的风险评分模型，有助于术前鉴别胆囊良恶性病变和评估肿瘤侵袭性[10] [11]。此外，利用术前放射影像数据建立的列线图(Nomogram)，能有效预测胆囊癌发生风险及手术难度，为外科医生提供有力的决策支持[12] [13]。

术前高危因素的精准评估是意外胆囊癌规范化诊疗的基础。通过整合患者的临床特征、影像学指标及生物标志物，建立科学的预测模型，可实现胆囊癌的早期发现，降低 IGBC 的发生率从而改善 GBC 患者的预后。

2.2. 影像学检查及其诊断价值

超声在早期胆囊癌与胆囊良性病变的鉴别诊断中占有重要地位，但对早期胆囊癌的敏感性较低，通常只能发现较明显的胆囊壁增厚[14]。超声造影(CEUS)可提示局灶性胆囊壁改变、内侧壁、外侧壁均匀性或不均匀性增厚、血管形态改变等，能更好地辨别胆囊壁增厚的良恶性[15]。此外，术中超声可较好地诊断胆囊癌浸润层次及侵犯肝脏的程度，其诊断早期胆囊癌的灵敏度和特异度分别可达 81%和 85%，敏感性优于术中快速冰冻病理活检[16]。CT 和 MRI 在评估肿瘤浸润深度和淋巴结转移方面显示出较高的诊断准确率。CT 对胆囊癌的敏感性高达 90%，但特异性相对较低，通过结合不规则病灶形态、脂肪间隙缺失及区域淋巴结肿大等影像学特征建立的风险评分，可有效区分恶性与良性病变[11]。相比于 CT，MRI 能更好地识别肿瘤大小、是否侵犯肝脏及胆管、是否有远处转移等。有证据表明，MRI 对胆囊癌淋巴结转移的敏感度可达 80%，对肝脏侵犯的敏感度可达 100%，优于 CT [17]。正电子发射计算机断层显像-CT (PET-CT)不仅能更好地鉴别胆囊良恶性病变，而且可更好地监测微小癌灶的全身转移情况。PET-CT 对胆囊癌淋巴结转移诊断的灵敏度达 93.8%，特异度达 70.4%，对胆囊癌远处转移诊断的灵敏度达 91.1%，特异度达 82.4% [18]。术中窄带成像(NBI)已被证实可辅助评估肿瘤的浸润深度和淋巴受累情况，敏感性优于传统 CT 和内镜超声，为术中决策提供支持[19]。结合多模态影像技术，如超声、CT、MRI 及 PET-CT 的联合评估，可显著提高术前胆囊癌的诊断率及分期准确性，为制定合理的手术方案提供依据。综上，多模态影像检查联合应用可提高 GBC 术前诊断率，从而降低 IGBC 的发生率，改善患者的预后。

2.3. 生物标志物及分子诊断的应用

目前，传统肿瘤标志物如 CA19-9、CA242、CA125、CEA 等在 GBC 术前诊断中的辅助作用有限，其敏感性和特异性均不足以单独用于筛查[20]。新兴的分子标志物和液体活检技术为 GBC 早期诊断提供了新的思路。利用血浆蛋白质组学检测，研究者已鉴定出一组差异表达蛋白，如 PAHX、CD8A、HRG 等，可在术前鉴别胆囊癌与胆囊炎，相关蛋白组合诊断准确率高达 94% [21]。循环游离 DNA (cf-DNA)等液体活检技术因其非侵入性和动态监测的优势，正在成为肿瘤早期诊断和疗效评估的重要工具，未来多标志物联合检测有望显著提高 GBC 术前诊断的敏感性和特异性[14]。随着分子诊断技术的进步，基于蛋白质组学、基因突变和免疫标志物的联合检测体系正在构建，有望实现胆囊癌的早期精准诊断和个体化治疗[21]。因此，生物标志物和分子诊断技术在 GBC 术前评估中具有广阔的应用前景，值得深入研究和临床

推广。

3. 根治性二次手术的时机与手术范围

3.1. 根治性二次手术的时机

IGBC 患者接受根治性二次手术的时间差异较大,中位时间为 2~3 个月,国内外尚未就实施胆囊癌根治性二次手术的最佳时间间隔达成共识[22]。过早二次手术术区的炎症会降低 CT 和 MRI 对重要解剖结构成像的准确率,不利于肿瘤分期和制定合理的手术方案,严重的腹腔粘连也会提高手术难度和相关风险。过晚二次手术可能因肿瘤恶性程度高及肿瘤扩散,失去根治性切除的机会[23]。Ethun 等认为,初次手术后 4~8 周内是 IGBC 患者接受延迟根治术的最佳时间[24]。另外有研究证实,2 周内接受再次手术的病人总体预后较好,并有望获得更好的远期疗效[25]。然而,许多研究指出,IGBC 患者的预后主要取决于肿瘤分期和残余病灶是否存在,与接受初次胆囊切除术和根治性二次手术间的时间间隔无关[26]-[28]。因此,经过充分术前评估明确肿瘤分期可行根治性手术者,应在初次手术后 2~8 周内实施根治性二次手术。

3.2. 腹腔镜与开腹手术的选择

已有多项研究证实,与开放手术相比,接受腹腔镜肝楔形切除或肝段切除术联合淋巴结清扫的可切除胆囊癌患者,在淋巴结清扫数量、切缘阴性率、穿刺孔转移/远处转移发生率和 3 年/5 年总体生存期等预后指标上无显著差异[29]-[32]。腹腔镜根治性二次手术预后不良的主要预测因素是 4~6 枚阳性淋巴结、超过 500 mL 的出血和残余病灶[32]。另有研究表明,选择腹腔镜或开放手术不是重要的预后因素,接受腹腔镜和开放式根治性二次手术的 IGBC 患者术后生存率比较差异无统计学意义[33]。并且,腹腔镜具有视野放大、更好的暴露程度、切口小等优势,在术中能够实现更加精细的解剖,更好地满足快速康复外科的要求,因而在术中出血量、住院时间和引流管拔除时间等方面均优于开放手术[34]。我们认为,在具备腹腔镜淋巴结清扫、肝切除和胆肠吻合术的专业知识和技能的微创肝胆胰中心,腹腔镜根治性胆囊切除术安全可行,其肿瘤学结局与开放手术无明显差异。但对于有胆囊破溃史、肿瘤已突破浆膜层或有明确肿瘤残留的患者,应谨慎实施腔镜手术。虽然最近的研究表明腹腔镜胆囊癌根治术的穿刺孔转移发生率下降至 10%,但是肿瘤突破胆囊壁和胆汁渗漏将使穿刺孔转移发生率增加 2 倍以上[35]。因此,腹腔镜术中应严格精细操作、保持胆囊壁的完整性和规范使用标本袋,实现全过程预防胆汁渗漏,避免穿刺孔转移和腹腔内播散转移。若胆囊与周围组织粘连严重、解剖不清而操作困难时不必勉强继续使用腹腔镜手术,可中转行开腹手术,不影响患者预后[20] [36]。

3.3. 手术方案选择

根治性切除术是 IGBC 患者获得治愈可能的唯一方法。术后病理分期是规范化手术治疗的重要依据,对于术中可疑 GBC 病人,应常规进行快速冷冻切片活组织病理学检查。术后应充分评估 IGBC 患者的肿瘤分期决定是否行需要行根治性二次手术,并依据术后病理分期选取手术方案。Tis 和 T1a 期胆囊癌患者接受单纯胆囊切除术即可达到 R0 切除,且 5 年生存率可达 100% [37]。因此,对于 IGBC 患者在确认胆囊管切缘阴性、术中无胆囊破损和胆汁渗漏时无需追加根治性二次手术。T1b 及以上分期 IGBC 患者残余病灶发生率较高,需接受根治性二次手术以改善患者预后[38]。然而,实施胆囊癌根治术时肝切除范围仍存在争议。先前的研究认为 T1b 和 T2 期 IGBC 患者实施肝楔形切除是合适的[39],但接受肝 IVb + V 段切除的 T2 期患者 5 年生存率更高。然而,有研究表明,T2 期胆囊癌患者接受肝楔形切除或肝 IVb + V 段切除的生存结局无显著差异[40]。另有研究发现,胆囊癌患者的肝转移常见于胆囊床周围,且 70% 的早期肝内微转移发生在 IVb 和 V 段,据此认为,肝 IVb + V 段切除是浆膜下浸润胆囊癌患者适宜的肝切除

范围[41]。由于术前难以通过影像学检查精准区分 T1b、T2a 和 T2b 期胆囊癌,即使是术中冷冻切片病理检查也不能完全明确肿瘤具体侵犯的解剖层次,因而建议 T1b~T2 期 IGBC 患者接受肝 IVb + V 段切除术,以保证肝切缘阴性。T3 和 T4 期胆囊癌患者往往术前即可明确诊断,意外胆囊癌患者较少见。对于 T3 期患者,可行不同程度肝脏切除、受累器官联合切除、扩大淋巴结清扫术,术后再辅以化疗、靶向等综合性治疗。T4 期因术前诊断较明确,IGBC 一般极少发生,此期已很大程度丧失根治性手术机会,治疗旨在提高病人生活质量,以姑息性手术联合多学科综合治疗为主。对伴有严重梗阻性黄疸者,可通过胆道内外引流术、内窥镜下支架置入或 B 超下放置引流管来改善症状。尚无确切证据证实扩大性胆囊癌根治术能使病人生存期获益。

4. 小结与展望

胆囊癌具有高度的侵袭性,易转移和复发,预后较差。应重视具有高危癌变因素的胆囊良性疾病患者的术前评估,结合影像学检查、生物标志物和分子诊断的多模态综合评估减少漏诊误诊,防止 IGC 的发生。术前多模态评估不仅提高了早期 GBC 的诊断率,也为后续的治疗决策提供了科学依据。这种多模态的诊断方法体现了精准医学的发展方向,促进了个体化治疗策略的制定。未来研究应更多聚焦于基于 IGBC 患者个体化特征的诊疗方案优化,通过大样本、多中心、前瞻性研究,形成 IGBC 规范化诊疗策略的共识,以达到基于 IGBC 病人实际情况的个性化治疗方案。

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