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## 重视意外胆囊癌的规范诊疗

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**摘要:** 意外胆囊癌是指因胆囊良性疾病行胆囊切除术后, 病理检查偶然发现的胆囊癌, 其术前漏诊率高、分期跨度大、治疗决策复杂, 是胆道肿瘤领域的重要挑战。本文结合当前证据, 系统梳理意外胆囊癌的流行病学、发病机制、诊断现状与治疗策略, 剖析当前诊疗瓶颈, 并从精准早诊、分子分型指导的个体化治疗、多学科协作模式构建等方面展望未来方向, 以期为临床实践与研究提供参考。

**关键词:** 胆囊肿瘤; 胆囊切除术; 诊断; 治疗学

### The standardized diagnosis and treatment of incidental gallbladder carcinoma should be taken seriously

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**Abstract:** Incidental gallbladder cancer (IGBC) refers to gallbladder cancer discovered incidentally during pathological examination after cholecystectomy for benign gallbladder diseases, and characterized by a high rate of missed diagnosis before surgery, wide staging variability, and complex treatment decision-making, IGBC poses a significant challenge in biliary tract oncology. With reference to existing evidence, this article systematically reviews the epidemiology, pathogenesis, diagnostic status, and treatment strategies of IGBC, analyzes existing bottlenecks in diagnosis and treatment, and proposes the future prospects from the aspects of precise early diagnosis, individualized treatment guided by molecular subtyping, and establishment of multidisciplinary collaboration models, in order to provide a reference for clinical practice and research.

**Key words:** Gallbladder Neoplasms; Cholecystectomy; Diagnosis; Therapeutics

胆囊癌(gallbladder cancer, GBC)是胆道系统最常见的恶性肿瘤,因早期症状隐匿、缺乏特异性筛查手段,多数患者确诊时已属中晚期,5年生存率不足10%<sup>[1]</sup>。意外胆囊癌(incidental gallbladder cancer, IGBC)是指因良性胆囊疾病(如胆囊结石、胆囊炎等)行胆囊切除的术中或术后病理检查中意外发现的胆囊恶性肿瘤。IGBC作为特殊类型GBC,因术前未明确诊断,其诊疗决策与预后受病理分期、手术范围等多种因素影响,临床处理更具复杂性。据统计,2020年全球每年约有10万例GBC新发病例,IGBC占有所有GBC的0.14%~1.6%<sup>[2-7]</sup>。而某些高发区(如南美安第斯山脉地区、印度北部)比例可高

达5%<sup>[8-9]</sup>。本文结合当前证据,系统梳理IGBC的诊疗现状,并探讨未来IGBC诊治的突破方向。

### 1 IGBC的诊断挑战与现状

1.1 术前漏诊困境 因GBC早期并无特异性临床症状,形态学改变也与慢性胆囊炎相似(如局灶性胆囊壁增厚、息肉样改变),且临床患者大多高度聚焦于既往“胆囊结石、胆囊息肉、胆囊炎等”主诉;部分临床医师经验不足,甚至术前并未完善增强CT及MRI、超声造影等影像学检查,导致GBC患者出现诊断延迟。超声、CT、MRI等影像学技术对T1期IGBC敏感度不足。常规腹部

超声由于受限于空间分辨率及操作者经验依赖性,在检测早期GBC(尤其是T1a期,肿瘤局限于黏膜层)时敏感度较低,容易漏诊微小病灶或误诊为胆囊良性病变。相比之下,多层螺旋CT增强扫描在评估T1b期(肿瘤侵犯至肌层)GBC时表现稍优,敏感度可达40%~50%,但对更早期病变的检出仍存在局限<sup>[10]</sup>。MRI凭借其优异的软组织对比度和多参数成像能力(如T<sub>1</sub>WI、T<sub>2</sub>WI及弥散加权成像),理论上能更清晰地显示胆囊壁层次结构及微小浸润,在早期GBC的检出上可能具有一定优势,但其检查费用较高、扫描时间较长,且对体内有金属植入物的患者存在禁忌,临床应用受到一定限制<sup>[11]</sup>。超声造影可将诊断敏感度提升至60%~80%(尤其≤2 cm的病灶),通过实时观察微循环灌注提高检出率,但普及率和标准化仍待推广。胆囊造影(如口服胆囊造影)因操作复杂、辐射风险已基本被弃用。肿瘤标志物如CEA(癌胚抗原)、糖类抗原19-9对IGBC的诊断特异性较差,约60%的T1期患者肿瘤标志物水平正常,而慢性胆囊炎患者中假阳性率可高达40%<sup>[12-14]</sup>。

**1.2 病理诊断时机** 术中冰冻病理是诊断IGBC的重要手段,但术中冰冻病理存在取样误差、制片质量、技术及时间压力、病理医生经验等因素,易漏诊或误诊。常规术后石蜡包埋切片通过充分固定、精细制片和多层面观察,能够提供更可靠的病理学信息,是目前IGBC确诊的关键依据和诊断金标准。病理诊断需注意以下关键点:首先,取材应覆盖胆囊全周,避免遗漏<sup>[5,15-18]</sup>;其次,需鉴别高级别异型增生与癌变,后者表现为细胞核异型性明显、核分裂象增多,可能已突破基底膜,存在间质浸润;最后,需结合免疫组化(如CK7、CK19、p53、CEA、MUC1、Ki-67)等明确诊断<sup>[19]</sup>。

**1.3 精准早诊技术** 液体活检[ctDNA(循环肿瘤DNA)、CTC(循环肿瘤细胞)]可捕获GBC特异性突变(如KRAS G12D),胆汁样本中微RNA(microRNA, miRNA)(如miR-21、miR-155)联合检测的敏感度超80%,有望成为胆囊结石患者术前筛查工具,提前识别高危癌变人群。一项前瞻性研究显示,对100例胆囊结石患者进行胆汁miR-21检测,发现该指标对IGBC的预测价值(受试者操作特征曲线下面积为0.88)显著优于传统影像学(受试者操作特征曲线下面积为0.65)<sup>[20]</sup>。

## 2 IGBC的流行病学与发病机制

**2.1 流行病学特征** IGBC发病率地域差异显著。在高发区(如印度、秘鲁、墨西哥),该比例可达2.5%~5.0%,而

在欧美发达国家则为0.5%~1.5%<sup>[8-9,21]</sup>。约70%以上的IGBC患者合并胆囊结石,显著高于普通人群,提示胆囊结石可能是重要的致癌危险因素<sup>[22]</sup>。“慢性炎症→异型增生→癌变”这一经典病理路径揭示了疾病发展的渐进过程<sup>[23-24]</sup>。值得注意的是,IGBC在女性中更为常见,男女比例约为1:2.5,且多见于50岁以上人群<sup>[7,25]</sup>。肥胖(体重指数≥30 kg/m<sup>2</sup>)作为独立危险因素,使IGBC风险增加2.3倍<sup>[9,21]</sup>;胆囊息肉(>1 cm)患者癌变风险为普通人群的5倍;原发性硬化性胆管炎患者患IGBC风险高达15%。此外,遗传因素如家族性GBC综合征导致IGBC的占比约为5%<sup>[26-27]</sup>。

**2.2 分子机制** IGBC呈多步骤致癌,常见KRAS(30%~50%)、TP53(20%~30%)、CDKN2A(15%~20%)等基因突变,且不同分期分子谱存在显著异质性<sup>[28-29]</sup>。早期(T1a期)以G1期黏膜内癌为主,主要表现为KRAS突变驱动的上皮增殖;而晚期(T2期以上)则伴浸润性生长与远处转移相关基因激活,如MET、EGFR通路异常<sup>[30-32]</sup>。分子分型研究提示,微卫星不稳定(microsatellite instability, MSI)和错配修复缺失(deficient mismatch repair, dMMR)在IGBC中占比5%~15%,为免疫治疗提供潜在靶点<sup>[33-34]</sup>。最新研究发现,IGBC中存在独特的“胆囊癌特异性甲基化谱”,如RASSF1A、CDH1等基因的启动子高甲基化,这些表观遗传改变在T1a期即可检测到,为早期诊断提供了新思路<sup>[28,35-37]</sup>。

## 3 IGBC的治疗策略

**3.1 手术决策** IGBC的手术决策基于准确的病理诊断,手术范围需基于病理TNM分期与患者一般情况做如下调整<sup>[38]</sup>。

(1)T1a期(局限于黏膜层)且无胆囊床浸润:单纯胆囊切除术已足够,5年生存率约85%。

(2)T1b期(侵犯肌层)或更高分期:需追加GBC根治性切除术(包括肝S4/5段切除、肝十二指肠韧带区域淋巴结清扫),但因多数患者初始手术未按肿瘤原则操作,二次手术残留/复发率高达30%~50%。一项回顾性研究显示,T1b期IGBC患者若未行二次根治术,5年生存率仅为55%,而行补充性根治性切除术者可达75%<sup>[39-40]</sup>。值得关注的是,对于腹腔镜胆囊切除术后延迟诊断的GBC患者,补救性根治性切除术后的5年生存率仍显著低于初始即接受规范的GBC根治术的患者<sup>[41]</sup>。

(3)手术方式选择需权衡患者全身状况、手术风险与预期生存获益,对于高龄、合并症多的患者,可考虑适

当缩小手术范围。

3.2 辅助治疗探索 对于T2~T4期IGBC患者<sup>[42]</sup>,术后辅助化疗(以吉西他滨+顺铂为主)可改善生存,但Ⅲ期临床试验证据稀缺,多数研究为回顾性分析。一项纳入120例T2期IGBC患者的多中心研究显示,接受辅助化疗组的中位总生存期为22个月,而未接受组为14个月。然而,化疗耐受性差,约40%患者因毒副反应中断治疗<sup>[43]</sup>。放疗因胆道邻近肝、胃等脏器,剂量限制显著,多用于局部晚期姑息。靶向治疗(如针对人表皮生长因子受体2阳性GBC的曲妥珠单抗)在IGBC中应用较少,缺乏高级别证据<sup>[44-45]</sup>。免疫治疗方面,程序性死亡受体1抑制剂在MSI-H(微卫星不稳定-高)/dMMR型IGBC中显示出初步疗效,客观缓解率达35%,但需进一步验证<sup>[46]</sup>。

3.3 分子分型指导的个体化治疗 基于下一代测序技术的分子图谱分析显示,IGBC可分为“干细胞样亚型”(富集SOX9、Notch通路,预后差)与“经典亚型”(ERBB、FGFR通路激活,对靶向药敏感),但目前尚无临床试验进行明确验证,未来需要更多前瞻性研究验证<sup>[46]</sup>。此外,可通过篮式试验筛选适合靶向药物(如FGFR抑制剂infigratinib)的患者<sup>[47]</sup>;免疫检查点抑制剂在MSI-H/dMMR型GBC中客观缓解率达30%~40%,需扩大样本验证在IGBC中的疗效<sup>[46]</sup>。

#### 4 IGBC的诊疗转变方向及建议

目前IGBC的诊疗缺乏高级别、系统化的循证医学支持。目前的治疗指南多基于回顾性研究,证据等级低,导致临床实践中存在大量争议和个体化差异。例如,对于T1b期IGBC,是否应行二次手术、手术范围如何界定、辅助治疗是否必要等问题,不同医疗机构的处理方式差异巨大。这种诊疗的不规范不仅影响患者生存质量,也造成医疗资源的浪费。

笔者团队提出IGBC诊疗的3个关键转变方向:

(1)从“机会性诊断”到“预防性筛查”:建立胆囊良性疾病患者的风险分层体系,将高危人群纳入定期筛查。具体而言,对胆囊结石患者(尤其是直径>1 cm者,病史>5年者、胆囊壁增厚>3 mm)、胆囊息肉患者(>1 cm)、肥胖患者、有家族史者,应纳入IGBC高危人群管理,通过无创检测(如miRNA、ctDNA)进行早期风险评估。

(2)从“经验性治疗”到“分子分型指导的精准治疗”:基于下一代测序技术的分子分型将IGBC分为“干细胞样亚型”(预后差)和“经典亚型”(对靶向药敏感),为治疗提供精准依据。未来,将建立IGBC的分子分型

数据库,指导临床选择最合适的治疗方案,避免“一刀切”的治疗模式。

(3)从“单一学科”到“多学科协作”:建立“外科-肿瘤-病理-影像-分子诊断”一体化诊疗团队,实现从术前评估到术后随访的全流程管理。术前通过人工智能辅助影像分析提高可疑病灶检出率(如基于深度学习的胆囊病变识别系统,敏感度提升至85%),术中推行“冰冻+多点活检+快速现场评价”减少漏诊,术后基于分子分型制订精准辅助治疗方案。在多学科协作模式下,IGBC的诊疗流程标准化,术前漏诊率可降至15%以下,T1b期患者二次手术率下降至20%。未来,将整合电子健康记录与人工智能分析平台,构建“从机会性诊断到主动性干预”的全流程管理模式,实现IGBC诊疗的精准化、个体化。通过多学科会诊机制,确保每例GBC患者都能获得最优的诊疗方案。

为实现上述转变,笔者团队提出了一些建议,详见表1。

#### 5 小结与展望

IGBC的诊疗现状深刻揭示了胆道恶性肿瘤管理中的根本性问题:早期准确诊断的缺失导致治疗时机的延误,而治疗策略的不规范又进一步影响了远期预后。不应满足于“偶然发现”的被动模式,而应构建“主动筛查-精准诊断-个体化治疗”的全链条管理体系。通过对IGBC诊疗现状的深入思考,发现其核心挑战不仅在于技术层面,更在于医疗理念和体系的革新。

IGBC反映出的GBC高漏诊率并非单纯技术问题,而是源于临床思维定式与医疗体系设计的双重局限。医生在面对胆囊结石、胆囊炎等常见良性疾病时,往往将注意力集中于解决“当前症状”,而忽视了潜在的恶性可能。这种“症状导向”的诊疗模式,使得GBC的早期预警机制形同虚设。同时,医疗资源分配失衡导致基层医疗机构缺乏必要的病理诊断和多学科协作能力,进一步加剧了GBC的漏诊和误诊。未来,将建立“胆囊结石患者筛查-高危人群评估-GBC早期干预”的三级防控体系,降低GBC漏诊和误诊率。

早期准确的诊断和规范化的治疗是提高IGBC远期疗效的关键。随着精准医学、人工智能、多学科协作等理念的深入应用,IGBC的诊疗将实现质的飞跃。未来5~10年,IGBC的诊疗将进入“预防-筛查-诊断-治疗-随访”的全链条规范化管理时代,IGBC术前漏诊率有望从90%以上降至20%以下,T1期IGBC比例显著提高,5年生存率有

表1 诊疗转变建议

Table 1 Recommendations for changes in diagnosis and treatment

建议	具体内容
构建GBC风险评估与筛查体系	1. 将胆囊结石、胆囊息肉等良性疾病的定期随访纳入常规管理,制订基于年龄、性别、肥胖程度、结石大小等因素的风险评分系统。 2. 开发适用于基层医疗机构的GBC筛查工具,如便携式miRNA检测设备,提高早期发现率。 3. 研发新型诊断技术,如基于人工智能的影像分析系统,提高早期诊断率。 4. 建立全国性IGBC登记系统,收集临床数据,为制订循证指南提供依据。
制订IGBC规范化诊疗指南	1. 由权威机构牵头,制订基于循证医学的IGBC诊疗指南,明确不同分期的手术指征、辅助治疗方案。 2. 建立IGBC的病理诊断标准,规范冰冻病理与常规病理的诊断流程。 3. 深入探索IGBC的分子机制,开发特异性靶点和生物标志物。 4. 制订IGBC术后随访方案,明确影像学检查与肿瘤标志物检测的频率和指标。
推动多学科协作诊疗模式	1. 在大型三甲医院设立GBC诊疗中心,整合肝胆外科、肿瘤内科、病理科、影像科等资源。 2. 建立远程会诊平台,将IGBC规范化诊疗模式推广至基层医院。 3. 开展多学科团队培训,提升各学科对IGBC的认识和协作能力。 4. 开展针对IGBC的临床试验,特别是针对“经典亚型”的靶向治疗和免疫治疗研究。
优化医疗政策与资源配置	1. 将IGBC的早期筛查纳入医保报销范围,提高患者筛查依从性。 2. 加大对IGBC研究的投入,设立专项科研基金。 3. 通过政策引导,促进医疗资源向IGBC高发地区倾斜。

望从目前的不足20%提升至50%以上。这一转变不仅将改善IGBC患者的生活质量和生存率,更将为整个恶性肿瘤的早期发现与精准治疗提供范例。GBC作为胆道系统最常见的恶性肿瘤,其诊疗模式的革新将推动整个胆道肿瘤诊疗体系的升级,最终实现从“被动治疗”到“主动防控”的跨越。

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