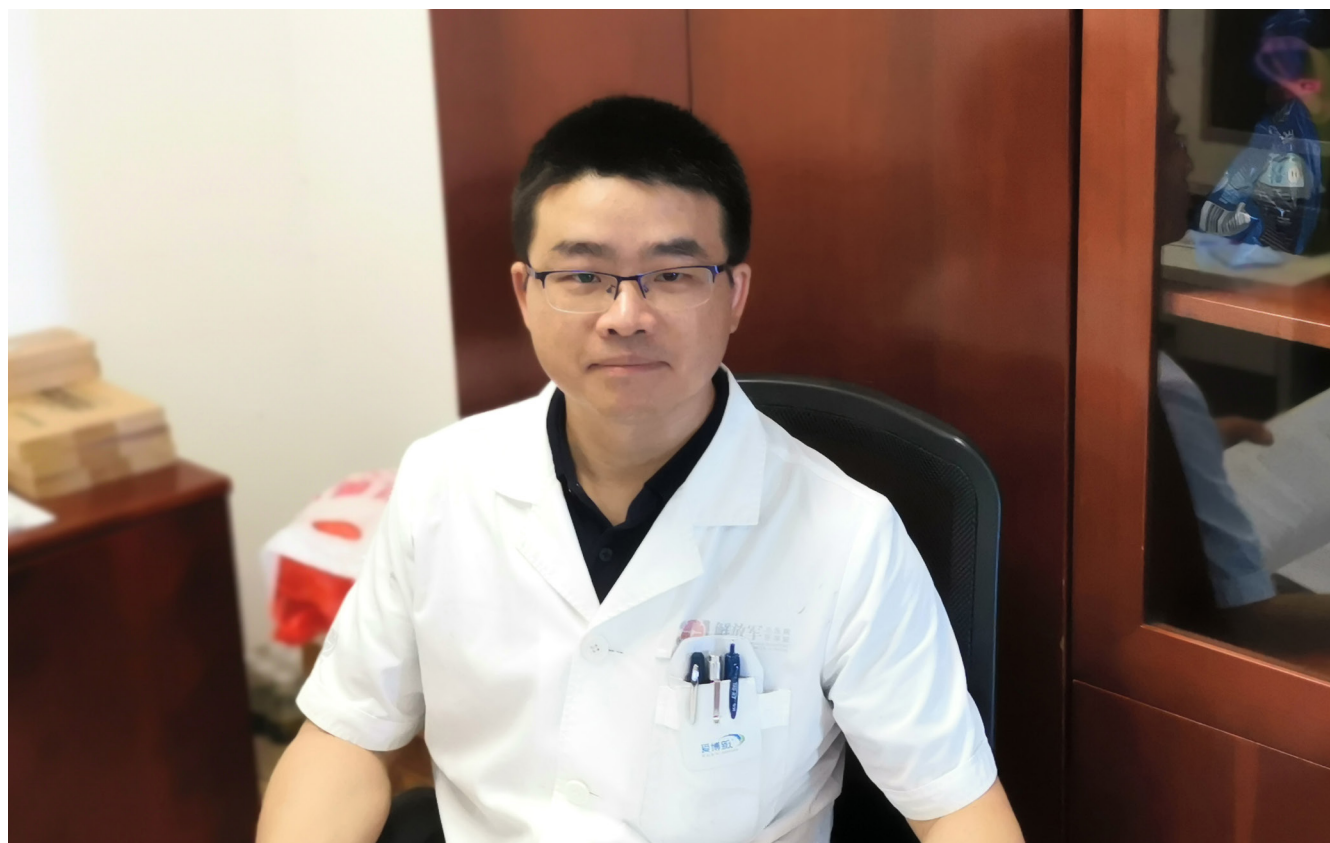


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**Shijie Huaren Xiaohua Zazhi**

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### 述评

- 1167 意外胆囊癌误漏诊原因与临床防治策略

秦建民

### 临床研究

- 1177 经口内镜下贲门缩窄术治疗胃食管反流病的疗效分析

王珏磊, 南寿山, 王超, 李朝霞, 窦广仙, 孙光斌

### 文献综述

- 1183 简述胃肠动力调节机制的研究进展

于红珍, 付明海, 吉小平, 额尼荣贵

- 1192 代谢性疾病的肠道菌群相关研究进展

李玉丽, 肖嫩群, 谭周进

### 临床实践

- 1200 经颈静脉肝组织活检术的临床应用

朱义江, 成德雷, 周春泽, 吕维富

- 1206 疑似恶性肿瘤的IgG4相关硬化性胆管炎5例临床分析

雷莉, 李丽, 宋文艳, 刘晖

- 1212 超声内镜与增强MRI术前联合判定直肠癌TN分期的应用价值

徐珊珊, 黄海涛, 徐建磊, 周华玲, 李阳

### 研究快报

- 1218 老年慢性功能性便秘患者认知性情绪调节策略和忧郁型人格行为分析

宋昌群, 张雨轶, 吴珍

## 消 息

- 1182 《世界华人消化杂志》性质、刊登内容及目标  
1205 《世界华人消化杂志》正文要求  
1211 《世界华人消化杂志》外文字符标准  
1217 《肠道微生物与消化系统疾病》书讯

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## Contents

Volume 28 Number 23 December 8, 2020

### EDITORIAL

- 1167 Causes of misdiagnosis and missed diagnosis and therapeutic and preventive strategies for unexpected gallbladder carcinoma  
*Qin JM*

### CLINICAL RESEARCH

- 1177 Efficacy of peroral endoscopic cardiac constriction for gastroesophageal reflux disease  
*Wang JL, Nan SS, Wang C, Li ZX, Dou GX, Sun GB*

### REVIEW

- 1183 Progress in research of gastrointestinal motility regulation  
*Yu HZ, Fu MH, Ji XP, E-Ni RG*
- 1192 Intestinal microflora in metabolic diseases  
*Li YL, Xiao NQ, Tan ZJ*

### CLINICAL PRACTICE

- 1200 Clinical application of transjugular liver biopsy  
*Zhu YJ, Cheng DL, Zhou CZ, Lv WF*
- 1206 IgG4-related sclerosing cholangitis suspected of being malignant tumors: A case series  
*Lei L, Li L, Song WY, Liu H*
- 1212 Application value of endoscopic ultrasonography combined with enhanced MRI in preoperative staging of rectal cancer  
*Xu SS, Huang HT, Xu JL, Zhou HL, Li Y*

### RAPID COMMUNICATION

- 1218 Cognitive emotional regulation strategy and melancholic personality behavior in elderly patients with chronic functional constipation  
*Song CQ, Zhang YY, Wu Z*

## Contents

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### COVER

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## 意外胆囊癌误漏诊原因与临床防治策略

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### Causes of misdiagnosis and missed diagnosis and therapeutic and preventive strategies for unexpected gallbladder carcinoma

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### Abstract

Laparoscopic cholecystectomy (LC) has been widely used in the treatment of gallbladder diseases. Since the indications for operation are constantly expanding, the intraoperative or postoperative incidence of unexpected gallbladder carcinoma (UGC) is gradually increasing.

The incidence of UGC in LC and open cholecystectomy is 2.09% and 0.91%, respectively. Because gallbladder carcinoma is often accompanied by gallstones or inflammation and lacks specific clinical manifestations, imaging features, and specific serum tumor markers, the preoperative diagnostic rate of gallbladder carcinoma is only 30%, and 30% of cases of gallbladder carcinoma are diagnosed intraoperatively or postoperatively. Pathological T stage, lymph node metastasis, and gallbladder rupture are independent risk factors for the prognosis of patients with UGC. Preoperative imaging combined with serological tumor markers, intraoperative careful exploration, and rapid pathological examination are important measures to reduce the misdiagnosis and missed diagnosis of UGC. For patients with benign gallbladder diseases with a high potential of canceration, performing cholecystectomy in time and strictly grasping the indications for preserving gallbladder for benign gallbladder diseases are important preventive measures to reduce the incidence of UGC.

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**Key Words:** Unexpected gallbladder carcinoma; Misdiagnosis and missed diagnosis; Causes; Treatment; Strategy; Prevention

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### 摘要

腹腔镜胆囊切除术(laparoscopic cholecystectomy, LC)已广泛应用于胆囊疾病治疗, 术中或术后意外发现胆囊癌逐渐增加, LC和开腹胆囊切除术意外胆囊癌

(unexpected gallbladder carcinoma, UGC)发生率分别为2.09%和0.91%。由于胆囊癌多伴有胆囊结石或炎症,早期缺乏特异性临床表现、影像学特征和特异性血清肿瘤标志物,术前胆囊癌确诊率仅30%,30%胆囊癌在术中或术后诊断。病理T分期、有无淋巴结转移、术中是否有胆囊破裂是影响UGC患者预后的独立危险因素。术前影像学联合血清学肿瘤标志物检查,术中仔细探查和快速病理检查,是降低UGC误漏诊的重要措施。对于存在高危因素的胆囊良性疾病患者,及时选择胆囊切除,严格掌握保胆指征,是降低UGC发生率的重要预防措施。

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关键词: 意外胆囊癌; 误漏诊; 原因; 治疗; 策略; 预防

**核心提要:** 术前影像学联合血清学肿瘤标志物检查, 术中仔细探查和快速病理检查, 是降低意外胆囊癌(unexpected gallbladder carcinoma, UGC)误漏诊的重要措施。对于存在高危因素的胆囊良性疾病患者, 适时选择胆囊切除, 是降低UGC发生率的重要预防措施。

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## 0 引言

随着生活水平的不断改善以及诊断技术的提高, 胆囊结石、息肉等疾病发病率逐渐增加, 因胆囊良性疾病行胆囊切除手术亦随之增加。腹腔镜胆囊切除术(laparoscopic cholecystectomy, LC)具有微创、术后恢复快等优点, 目前已经成为胆囊良性疾病手术切除的首选方法, 近年来LC技术已广泛应用临床, 术中或术后意外发现胆囊癌发生率逐渐增加。意外胆囊癌(unexpected gallbladder carcinoma, UGC)是指临床上因胆囊良性疾病行胆囊切除, 术中或术后偶然发现的胆囊癌。LC UGC的发生率为0.2%-2%, 占胆囊癌总数50%<sup>[1,2]</sup>。国内LC术中和术后UGC发生率为0.17%-0.34%<sup>[3]</sup>, 低于国外0.22%-0.84%<sup>[4,5]</sup>。70%胆囊癌发生与胆囊结石有关, 胆囊结石患者胆囊癌危险度是无结石患者的13.7倍, 由于胆囊癌多伴有胆囊结石或炎症, 缺乏特异性临床表现和血清肿瘤标志物, 导致30%胆囊癌在术中或术后诊断<sup>[6,7]</sup>, 术前胆囊癌确诊率仅30%, 胆囊癌恶性程度高, 较早出现淋巴结转移和侵犯邻近脏器, 手术切除率低, 5年生存率不足5%<sup>[8-10]</sup>。由于UGC手术仅按胆囊良性疾病切除胆囊, 未按恶性肿瘤原则处理, 术后容易导致肿瘤种植、转移淋

巴结肿瘤残留等问题, 严重影响预后。因此早期发现胆囊癌, 减少误漏诊发生, 对UGC选择合理的治疗方法, 是提高胆囊癌疗效和改善预后的关键。

## 1 UGC的临床特点与早期诊断

**1.1 UGC误漏诊原因** 胆囊癌发病隐匿, 70%以上合并胆石症, 而胆石症患者胆囊癌发生率为4.5%-14%, 27%-41%胆囊癌患者是以UGC形式被发现<sup>[11,12]</sup>。超过1%急性胆囊炎患者并发胆囊癌, 非急性胆囊炎中胆囊癌发生率为0.4%, 以急性胆囊炎为临床表现患者中UGC的发生率高于非急性胆囊炎患者, 急性炎症临床表现极易掩盖胆囊癌的临床表现和影像学表现, 导致术前UGC误漏诊<sup>[13,14]</sup>。术前准备时间短、检查不够充分, 是UGC发生误漏诊的主要原因之一。胆囊结石或息肉合并胆囊炎症时B超、计算机断层扫描(computed tomography, CT)和/或磁共振成像(magnetic resonance imaging, MRI)对胆囊壁内微小病灶、胆囊壁厚度、胆囊壁与周围组织的界限显示欠清晰, 易掩盖胆囊癌早期的影像学特征。胆囊息肉样病变分为肿瘤性(腺癌和腺瘤)和非肿瘤性(炎性息肉、胆固醇息肉、腺肌增生等), 胆囊腺瘤癌变率为10%-19.3%<sup>[15]</sup>。目前影像学 and 血液肿瘤标志物等尚不能判断胆囊息肉样病变是否恶变, 而且腹腔镜手术中医生对胆囊病变无触觉感, 尤其胆囊癌早期病变未侵犯浆膜层时, 术中更难以发现异常。若存在急性炎症、充血、水肿、粘连等病理变化时, 术前、术中诊断更加困难、容易误漏诊。

**1.2 重视术前影像学 and 肿瘤标志物检查在早期胆囊癌诊断中的作用** 超声简便易行、敏感性高, 是诊断胆囊疾病的首选检查方法, 准确率与检查设备、操作医生技术和临床经验密切相关。增强CT与MRI、磁共振胰胆管成像(magnetic resonance cholangiopancreatography, MRCP)检查能客观反映胆囊与胆管影像全貌和邻近脏器关系, 对临床治疗方案的制定具有重要参考价值。胆囊癌早期检出率仅为8.3%, 超声、CT、MRI诊断准确率分别为63.8%、58.3%、72.2%, 超声、CT和MRI联合诊断准确率为86.1%。超声及MRI对胆囊腔内病变显示优于CT。CT、MRI对合并周围脏器浸润的显示较超声清晰, MRI能够更加敏感分辨血管及肿大淋巴结<sup>[16]</sup>。早期胆囊癌尤其合并结石者, B超诊断的敏感性下降, 仅为53%, 彩色多普勒超声对小结节型胆囊癌, 以最大血流速度 $V_{max} \geq 0.2$  m/s作为判断恶性病变的指标, 敏感性为81.8%, 特异性为98.5%, 准确性为96%; 若以阻力指数 $RI > 0.6$ 作为判断恶性病变的指标, 其敏感性为72.7%, 特异性为98.5%, 准确性为94.7%<sup>[17,18]</sup>。超声造影(contrast-enhanced ultrasonography, CEUS)诊断胆囊癌符

合率为92.31%, 优于彩色多普勒超声, CEUS对于肿瘤性壁增厚的胆囊癌诊断敏感性、特异性、准确率分别为84.6%、100%、98.4%<sup>[19,20]</sup>。谐波对比增强超声内镜(contrast-enhanced harmonic endoscopic ultrasonography, CEH-EUS)对壁厚型胆囊癌诊断的敏感性、特异性、准确率分别为89.6%、98%和94.4%, 敏感性高于超声内镜(endoscopic ultrasonography, EUS); CEH-EUS对胆囊恶性结节样病变诊断的敏感性、特异性、准确率分别为100.0%、94.4%和95.8%, 表明CEH-EUS对于区分胆囊良恶性病变具有重要的临床应用价值<sup>[21,22]</sup>。CEH-EUS对直径大于1 cm息肉样胆囊癌诊断的敏感性和特异性分别为93.5%和93.2%优于EUS(90%、91.1%)<sup>[23]</sup>。增强CT对胆囊癌诊断符合率为84.35%, 与超声相比, CT在胆囊癌和慢性胆囊炎、胆囊息肉的鉴别诊断以及临床分期和可切除性判断等方面具有更强的优势, 对胆囊癌的总确诊率高于超声<sup>[24]</sup>。MRI对胆囊癌术前诊断符合率为91.57%, 肝脏直接浸润诊断符合率为70.45%, 淋巴结转移敏感性为64.51%, MRI弥散加权胆囊癌的诊断敏感性和特异性分别为83.3%和100%<sup>[25,26]</sup>。MRI结合MRCP更能敏感地显示胆囊癌及其与邻近脏器受累情况, 清晰地显示肝内外胆管受累所致胆道梗阻征象, 有利于准确评估肿瘤局部浸润范围。MRI在区分胆囊癌T1期(肿瘤局限于黏膜层)和T2期(肿瘤局限于黏膜肌层)敏感性(84.9%)优于CT(83.9%)和EUS(79.5%)<sup>[27,28]</sup>。正电子发射断层扫描(positron emission tomography, PET)-CT作为一种功能及解剖显像, 胆囊癌诊断准确率为95.9%, 淋巴结转移为85.7%, 远处转移为95.9%, 术后局部残余癌诊断敏感性和特异性分别为78%和80%, 表明PET-CT对胆囊癌诊断、淋巴结、远处转移和疗效评估具有重要价值<sup>[29,30]</sup>。浸润型胆囊癌误漏诊率最多, 为63.16%, 与病灶较小、侵及肌层, 影像学检查早期难以清晰发现有关; 结节型胆囊癌易将病灶误认为是结石、息肉, 肿块型胆囊癌易误诊为胆汁分层改变<sup>[31]</sup>。

目前胆囊癌缺乏一种特异性公认的血清学肿瘤标志物, 虽然现有的一些血清学肿瘤标志物对胆囊癌早期诊断缺乏特异性, 但这些肿瘤标志物表达水平的异常对早期胆囊癌的诊断具有一定参考价值。CA242对胆道恶性肿瘤的敏感性优于CA19-9、CEA, 其敏感性、特异性分别为84%、98.7%, 是目前已知的胆道肿瘤最敏感肿瘤标志物<sup>[32,33]</sup>。CA19-9对胆囊癌诊断阳性率为32%, CEA对胆囊癌诊断阳性率为26%, 二者联合检测阳性率为64%<sup>[34]</sup>。术前CEA、CA19-9双阴性组、单独CA19-9阳性组、单独CEA阳性组和CEA、CA19-9双阳性组的胆囊癌患者R0切除率分别为86.1%、73.1%、71.4%、45.1%, 术后5年生存率分别为36.7%、5.6%、9.5%、0,

其中CEA、CA19-9双阴性组患者R0切除率较高、预后最好, 建议积极行根治性手术治疗, 而CEA、CA19-9双阳性组患者R0切除率偏低、预后较差, 且常合并有临近脏器和淋巴结转移, 是否需要行扩大性手术切除范围需要综合评估, 谨慎选择<sup>[35]</sup>。四个标志物联合检测有助于胆囊癌早期诊断、治疗效果和预后评估<sup>[36]</sup>。超声联合血清CA19-9、CEA诊断胆囊癌敏感性为90%, 特异性92%, 高于单纯B超或血清CA19-9、CEA检查<sup>[37]</sup>。术前血清CA125和CA19-9水平高的胆囊癌患者中位生存时间明显短于低水平者( $P<0.05$ ), 但术前血清CEA水平与总体生存时间无关( $P>0.05$ ), 术前血清CA19-9及CA125可以作为胆囊癌诊断及预后判断指标<sup>[33,38]</sup>。影像学联合血清学肿瘤标志物检查, 对于提高胆囊癌早期检出率, 降低UGC发生率, 具有重要的临床应用价值。

## 2 术中仔细探查和快速病理检查是降低UGC误漏诊的重要措施

对于高危的胆囊癌患者, 尤其术前影像学或/或血清肿瘤标志物异常, 高度怀疑胆囊癌的患者实施胆囊切除术, 应仔细操作, 尽可能避免术中胆囊破裂、胆汁外溢情况发生, 如果局部炎症粘连严重, LC操作切除困难, 及时中转开腹, 保证胆囊切除的完整性, 术中对肝脏结节或肿大淋巴结获取组织病理检查。UGC的诊断主要依赖于手术中病理检查。术中发现胆囊内有肿块或胆囊壁有浸润性或增厚性改变时应快速冰冻病理检查, 术中快速病理检查诊断胆囊癌的特异度和灵敏度分别为100%和65%, 对于胆囊原位癌诊断率为42%<sup>[39,40]</sup>。因此术中发现胆囊异常, 胆囊切除后标本均应常规剖开检查, 仔细观察和触摸胆囊壁有无异常肿块、硬结以及局限增厚情况, 胆囊黏膜是否规则、完整, 有无溃疡、中断、增厚突起、皱缩变硬, 胆囊黏膜有无灰白色颜色改变, 和乳头状物附着等。病变处或可疑病变处组织多点全层取材, 尤其病变与胆囊粘膜交汇处组织, 减少漏诊率, 提高快速病理准确率。

## 3 UGC治疗方法的选择

3.1 术中或术后病理分期是选择UGC治疗方法的重要依据 由于胆囊壁生理解剖结构特殊, 仅有黏膜层与肌层直接相连, 而无黏膜下组织, 且肌层薄弱, 使胆囊癌易侵犯肌层而突出浆膜外, 造成周围局部组织器官受<sup>[41,42]</sup>。15%-20%胆囊癌是在术中探查或术后病理检查发现, 而在胆囊癌得到确诊时, 仅有20%患者病变局限于胆囊壁内, 80%已侵犯临近组织或出现远处转移<sup>[43]</sup>。胆囊癌患者预后与肿瘤是否R0切除、淋巴结转移、病理T分期、血管侵犯等因素密切相关, 由于初次手术仅行单纯



胆囊切除缺乏淋巴结、临近脏器是否有转移等资料, 无法完成TNM分期准确评估, 因此将病理T分期作为UGC危险因素评估和治疗方法选择的重要依据<sup>[44-46]</sup>. TNM分期中原发肿瘤T分期<sup>[47]</sup>: (1)Tis为黏膜原位癌; (2)T1为肿瘤侵犯黏膜固有层(T1a)或肌层(T1b); (3)T2为肿瘤穿透肌层, 但未侵犯浆膜或肝脏; (4)T3为肿瘤穿透浆膜层, 或直接侵犯肝脏和(或)一个邻近器官; (5)T4为肿瘤侵犯门静脉主干或肝动脉, 或直接侵犯两个或以上肝外器官. UGC中T2期肿瘤最常见, 占47%, T3期与T1期分别位25.1%、23%, T4期与Tis期较少见, 分别为4.2%、2.4%<sup>[47]</sup>. 由于术中冰冻病理检查取材范围局限性, 不可能涉及整个胆囊壁, 而且冰冻病理检查难以区分黏膜不典型增生与胆囊局灶癌变, 导致术中冰冻病理检出癌细胞灵敏度为64%-84.2%, 灵敏度随肿瘤浸润深度增加而增加. 术中冰冻病理检查评估Tis期灵敏度为40%, T2及T3期肿瘤灵敏度为83%, 术中冰冻病理检查对癌细胞侵犯深度的评估准确性为70%-85.7%, 对胆管切缘阳性诊断误差率为25%<sup>[48-50]</sup>. 胆囊癌淋巴结转移与肿瘤浸润深度(T分期)密切相关, 淋巴结转移和淋巴管侵犯在T1b期中分别为15.7%、18.4%, T2、T3、T4期淋巴结转移阳性率随T分期逐渐增加, 分别为46%-48%、72%和80%, 淋巴结转移程度与患者预后明显相关, pN0、pN1、pN2及pN3期胆囊癌患者5年生存率分别为60.3%、30%、16.8%及5.9%; T1a期、T1b期、T2期、T3期患者5年累积生存率分别为95.7%、90%、75%、40%, 随T分期和淋巴结转移增加胆囊癌生存率逐渐降低<sup>[51,52]</sup>. UGC行LC后肿瘤复发和腹膜种植发生率为10%-29%, 胆漏发生率为22%, 癌细胞可能会通过漏出的胆汁种植于腹膜、大网膜、皮肤切口或其他器官表面, 造成腹腔种植转移或切口转移, 胆囊破溃胆汁漏出是切口及腹膜转移的主要原因, 是影响Tis及T1期UGC预后的重要因素<sup>[53-57]</sup>. 病理T分期、有无淋巴结转移、术中胆囊破裂是影响UGC患者预后的独立危险因素<sup>[52]</sup>, 因此术中或术后病理分期是评估UGC严重程度和制定治疗方案的客观依据.

3.2 坚持循证医学原则, 合理选择UGC治疗方法 术中或术后发现UGC, 依据术中探查情况、淋巴结和肿瘤组织病理检查结果, 需要术中及时中转开腹或腹腔镜胆囊癌根治切除术, 以及术后再次行胆囊癌根治性手术. Tis期、T1a期胆囊癌肿瘤未侵及肌层, 淋巴结转移率为2.5%, 84%UGC患者行单纯胆囊切除术, 其中46%采用LC, 单纯胆囊切除术后肿瘤复发率为1.1%-3.7%, 5年生存率为90%-100%<sup>[57,58-60]</sup>. 术中胆囊完整切除, 无破溃及胆汁溢出, 单纯切除胆囊即达到根治效果, 无需常规行胆囊床肝脏楔形切除和肝十二指肠韧带淋巴结清扫, 术后1、3、5年累计生存率分别为100%、96.2%、

96.2%<sup>[61-63]</sup>. T1b期UGC侵及胆囊肌层, 胆囊床侧胆囊没有浆膜层, 癌细胞通过胆囊静脉回流入肝脏致肝床微转移, 肿瘤肝床微转移距离不超过1.6 cm, 需行距胆囊床2 cm以上肝组织切除, 获得肿瘤根治性切除. 淋巴结转移首先累及胆囊三角淋巴结及沿胆总管分布的淋巴结, 淋巴结转移率15.7%, 淋巴管浸润率为18%. 术中常规行13a淋巴结活检, 若13a淋巴结活检阴性, 行12组和8组淋巴结清扫; 若13a淋巴结活检阳性, 则行扩大淋巴结清扫, 包括12组、8组、13组和9组淋巴结<sup>[64,65]</sup>. T1b期UGC患者术后1、3、5年累积生存率分别为100%、89.7%和82.8%. T1b期胆囊癌根治术后淋巴结转移率仅为1.4%, 扩大切除并未增加T1b期胆囊癌的长期生存率, 根治切除术后5年生存率为83.3%, 与开腹胆囊切除、LC术后5年生存率84.4%、68.8%相比, 无显著性差异( $P>0.05$ )<sup>[59,66-69]</sup>. 但多数研究发现T1b期UGC出现淋巴管、神经侵犯发生率分别为12%、2.5%, 远高于T1a期的2.5%、0.4%. T1b期UGC行单纯胆囊切除术后肿瘤残留发生率为10%, 胆囊癌根治手术使T1b期胆囊癌5年生存率由42%增加为79%, 肿瘤复发率由24.5%降低为8.6%, 差异具有显著性( $P<0.05$ )<sup>[59,67]</sup>. 因此基于T1b期UGC病理和生物学行为特点, 笔者认为对于T1b期UGC行胆囊癌根治性切除术是合理的选择.

T2期UGC侵犯胆囊肌层及周围结缔组织, 但未突破浆膜层或未侵及肝脏, 胆囊癌细胞经胆囊静脉回流入肝脏, 回流肝脏范围距胆囊床2-5 cm, 且至少有1个方向范围 $>4$  cm. 31% T2期胆囊癌患者合并肝转移, 因此对于T2期UGC患者常规行肝脏IVb和V段切除<sup>[65,70]</sup>. T2期UGC中将胆囊腹腔游离侧肿瘤分为T2a期, 肝脏侧分为T2b期, T2a期淋巴结转移、神经侵犯和血管侵犯概率远低于T2b期胆囊癌. T2a期UGC患者接受根治性切除术5年生存率(70.5%), 与未行肝切除的患者(54.8%)无显著性差异, 而T2b期UGC患者行根治性切除术后5年生存率为80.3%, 明显高于未行肝切除30%; T2a期胆囊癌术后3年、5年存活率(73.7%、64.7%)显著高于T2b期(52.1%、42.6%), T2a期胆囊癌预后优于T2b期胆囊癌<sup>[71,72]</sup>. T2期胆囊癌中神经浸润发生率为25%-35%, 淋巴结转移率为19%-62%, 术中先行16组淋巴结病理检查, 若为阳性表明已有远处转移, 仅行姑息治疗; 若16组淋巴结阴性, 再行13a组淋巴结活检, 13a组淋巴结活检阳性者, 则行8组、12组、13a组、9组淋巴结和神经纤维组织清扫; 13a组淋巴结活检阴性者, 需要清扫8组、12组淋巴结和神经纤维组织; T2期胆囊癌患者术中行淋巴结清扫和未清扫术后5年生存率分别为50%、10%, 有显著性差异( $P<0.05$ )<sup>[65,73,74]</sup>. 由于T2期UGC行单纯胆囊切除术后肿瘤残留率为40%, 单纯胆囊切除术后5年生

存率显著低于胆囊癌根治术(38% vs 78%), 胆囊癌根治性切除术显著提高T2期UGC患者生存率<sup>[75-77]</sup>, T3期UGC神经浸润发生率为25%-35%, 36.4%患者出现肝脏转移, 淋巴结转移发生率为45%-70%, 肿瘤残留发生率为36%, 单纯胆囊切除术后5年存活率(8%-19%)显著低于胆囊癌根治术(34%-40%)<sup>[74,78,79]</sup>, 因此T3期胆囊癌需行胆囊癌扩大根治术, 包括胆囊肿瘤切除、受累部分肝脏切除、临近脏器组织联合切除及淋巴结清扫, 达到R0切除的T3期胆囊癌患者术后5年生存率可达到60.6%<sup>[80,81]</sup>。由于T4期胆囊癌肿瘤累及临近或远处多个脏器组织, 淋巴结转移率高达67%-80%, 预后差, 但对于部分患者可行扩大性根治性手术, 包括受累肝脏的半肝以上切除、联合临近受累脏器、动脉或静脉切除、扩大淋巴结范围清扫, 可改善其预后<sup>[80,82]</sup>。对于UGC是否需要肝外胆管切除, 与肿瘤部位、胆囊管切缘是否受侵有关, 如果术中发现肿瘤累及胆囊管或病理检查胆囊管残端肿瘤残留, 则需要肝外胆管切除。对于胆囊颈部或胆囊管癌患者, 胆囊管癌易经肝十二指肠韧带侵犯至胰头、主动脉旁淋巴组织及肝脏Glisson鞘, 胆囊管癌对周围神经、淋巴结/管、血管的侵犯比例明显高于胆囊底、体部癌, 胆囊管癌3、5年生存率明显低于胆囊底、体部癌, 胆囊管癌要比同期的其它部位胆囊癌手术范围更大, 无论任何分期均需要行联合肝外胆管切除的胆囊癌根治术, 降低术后复发率, 改善预后<sup>[83,84]</sup>。

术后发现UGC需要再次手术的胆囊癌患者, 再次手术的时机一直是临床医生关注的问题。肿瘤的转移发生在第1次手术后30 d内, 建议再次手术间隔时间为第1次手术后6 wk内<sup>[64,85]</sup>。虽然Butte等<sup>[86]</sup>研究发现UGC首次行胆囊切除术与二次切除的时间间隔长短对预后无明显影响, 首次手术方式(LC、开腹胆囊切除、LC+中转开腹、剖腹探查等)对再次根治性切除患者生存率无显著影响, 但大多数研究认为再次手术应在初次手术后1-4 wk内实施为宜<sup>[87,88]</sup>。Du等<sup>[89]</sup>分析UGC术后2 wk内、2 wk-1 mo和超过1 mo再次行根治性手术, 结果发现2 wk内再次手术术后1、3、5年累积生存率分别为94.6%、69.6%和41.4%( $P<0.01$ ), 但2 wk-1 mo和超过1 mo再次行根治性手术后生存期之间无显著性差异( $P>0.01$ ), 2 wk内再次手术术后生存期优于2 wk后手术, 建议UGC再次手术时间宜在2 wk内进行, 延迟手术可使肿瘤播散, 失去根治性手术机会。孟强芳等<sup>[90]</sup>研究发现UGC术后生存期与初次手术T分期、病理分化程度、有无病灶残留、二次术后N分期及切缘有关, 而与性别、年龄及二次手术时间无关, 初次手术有无病灶残留和二次术后手术切缘是影响UGC预后重要因素。无病灶残留UGC患者预后与二次手术时间无关, 但对有病灶残留的UGC

患者, 手术时间越早, 患者预后越好, 二次手术力求达到R0切除。术后依据病理分期决定是否需要化疗和/或局部放疗, 对于无法根治性切除的患者术后依据肿瘤生物学行为和基因检测结果, 针对高肿瘤负荷、高微卫星不稳定性、DNA错配修复的UGC患者, 联合化疗、分子靶向药物、pembrolizumab单抗、放疗等综合性治疗, 延长患者生存期。

#### 4 心理支持在UGC患者康复中具有不可忽视的重要作用

LC或开腹胆囊切除术后发现UGC, 患者在术后短期内需要接受第二次手术, 短期内再次手术作为一种强烈的心理应激源, 导致患者紧张、恐惧、焦虑和悲观等不良心理反应, 严重者出现失眠、食欲减退、失去生活信心等负面情绪, 这种心理状态直接影响患者术后康复和疗效, 因此根据患者心理状态评估, 制定针对性心理干预计划, 通过耐心、细致的心理疏导, 解答患者提出的各种问题, 消除内心疑虑、恐惧和悲观情绪, 提高患者对疾病以及再次治疗手术方式的了解, 建立良好的支持性家庭社会关系, 消除紧张、焦虑的负面情绪<sup>[91]</sup>。有效的心理支持可消除患者的心理问题, 通过音乐疗法、心理暗示法、转移注意力法等缓解患者负性情绪, 必要时让手术成功UGC患者面对面分享经验, 帮助患者树立治疗信心, 增强患者对抗疾病的信心<sup>[92]</sup>。

#### 5 重视胆囊癌的早期预防, 降低UGC发生率

国内胆囊癌伴发胆囊结石为20%-82.6%, 国外胆囊癌伴发胆囊结石为54.3%-100%, 胆囊结石患者发生胆囊癌危险度是无胆囊结石的13.7倍, 结石<1 cm患癌概率为1%, 结石2-2.2 cm为2.4%, 结石>3 cm为10%, 胆囊结石反复机械刺激、合并细菌感染、胆汁中毒素刺激诱发胆囊癌发生<sup>[93-95]</sup>。胆囊腺癌占胆囊息肉样病变8.4%-16.4%, 胆囊腺瘤的癌变率为19.3%-58.8%<sup>[96,97]</sup>。胆囊息肉病变直径>14.5 mm应高度怀疑癌变, T1期胆囊癌病变平均直径为20.5 mm±5.8 mm, 超过27 mm则可能在T2期及以上, 表明胆囊息肉样病变大小与胆囊癌发生有一定的相关性<sup>[98]</sup>。胆囊腺瘤直径>1 cm腺瘤恶变几率更高, 胆囊腺肌病为癌前病变, 具有癌变倾向<sup>[99,100]</sup>。

胆囊癌发生的高危因素<sup>[101,102]</sup>: (1)年龄≥60岁, 慢性胆囊炎、胆囊结石病史≥10年, 疼痛反复发作; (2)胆囊充满型结石或结石占据胆囊腔50%以上, 结石直径≥2 cm; (3)长期胆囊结石伴胆囊萎缩, 或伴胆囊壁增厚、钙化, 尤其瓷化胆囊; (4)单个广基、无蒂的息肉, 直径>1 cm, 近期明显增大; (5)胆囊结石合并胆囊息肉; (6)糖尿病合并胆囊结石, 反复发作; (7)胆囊腺肌症、胆囊黄色肉芽肿性胆囊炎、胆囊腺瘤。对于胆囊结石或/和胆囊

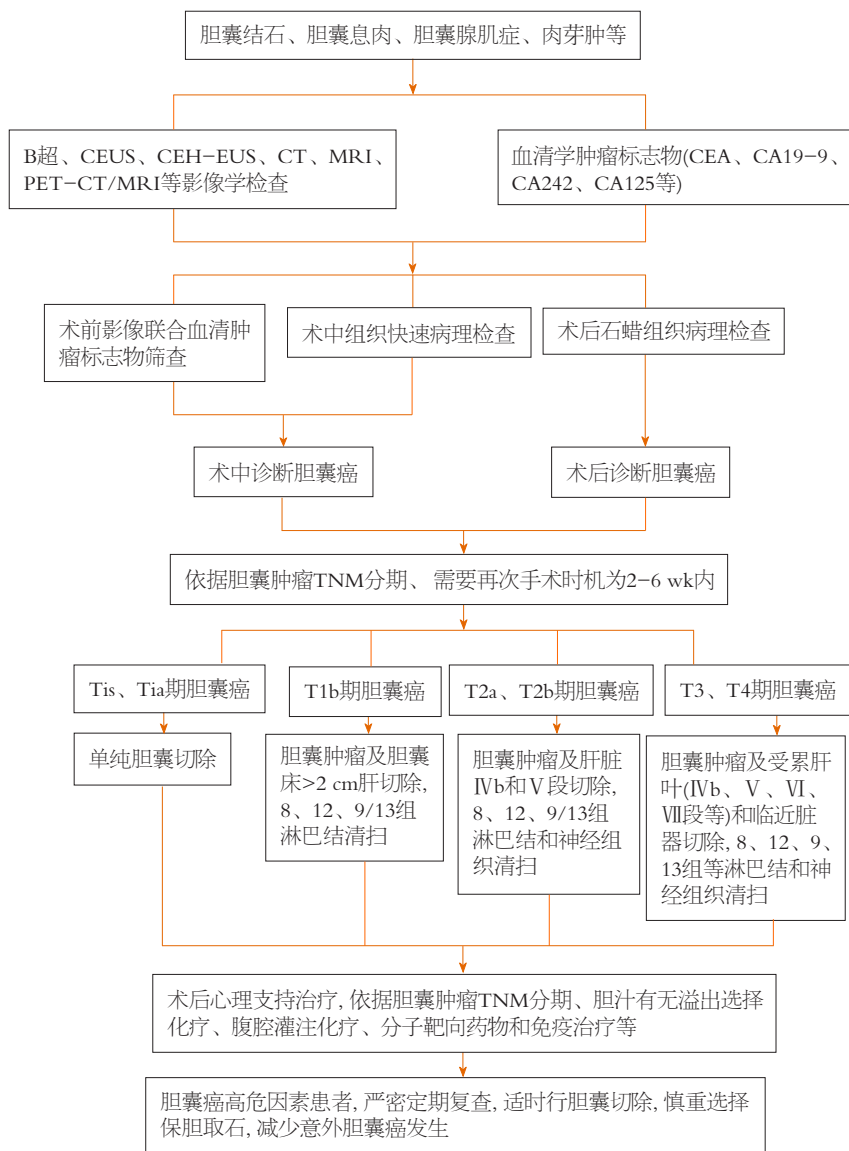


图1 意外胆囊癌临床诊治流程. CEUS: 超声造影; CEH-EUS: 谐波对比增强超声内镜; CT: 计算机断层扫描; MRI: 磁共振成像; PET: 正电子发射断层扫描.

息肉患者腹痛失去原有的诱因与规律性, 疼痛时间明显延长; 无症状的胆囊息肉、萎缩性胆囊炎近期出现明显持续性疼痛; 明显的饮食减少、乏力、体重下降而又排除胃肠道疾病等情况时, 应警惕胆囊癌变发生<sup>[103]</sup>. 对有高危因素的胆囊良性疾病患者, 应做到术前结合B超、CEUS、CA19-9、CA125、CEA等进行初步筛选, 必要时行CT、MRI、CEH-EUS、PET-CT等影像学检查进行定位诊断, 以实现早期诊断胆囊癌. 对于结石性萎缩胆囊炎、瓷化胆囊或直径1 cm以上的胆囊息肉、腺瘤、腺肌症, 以及胆囊结石合并胆囊息肉者, 不管息肉大小或有无症状, 因为胆囊结石反复刺激胆囊黏膜和息肉, 双重危险因素会增加胆囊癌发生, 均应积极行预防性胆囊切除, 降低胆囊癌的发生率.

胆囊具有储存、浓缩胆汁和收缩功能, 以及复杂的

化学和免疫功能, 胆汁进入胆囊进行存储和浓缩(浓缩后的胆汁比肝胆汁浓缩30倍), 胆囊具有重要的调节消化功能, 胆囊切除术后胆汁持续排入肠道, 因此胆汁返流性胃炎的机会增加, 进食时无足够的胆汁, 影响肠道消化降解及细菌调节功能, 从而引起消化不良、腹胀、腹泻等症状<sup>[104]</sup>. 另外胆囊切除术后胆盐代谢异常和自主神经功能紊乱, 胆道压力改变使胆管内流体压力失去了缓冲作用, 导致胆总管内压力增高, 引起胆总管代偿性扩张, 胆汁容易在胆管内形成涡流产生结石. 胆汁压力改变、涡流形成及胆汁返流引起胆管下端局部慢性炎症水肿, 导致Oddi括约肌狭窄和缩窄性 Vater乳头炎, 引起腹痛等症状<sup>[105]</sup>. 胆囊切除术后胆管损伤发生率为0.6%-1.5%, 因胆管损伤所致病死率为6%<sup>[106,107]</sup>. 胆囊切除术后结肠癌发生危险性增加1.34倍, 尤其右半结肠癌



增加1.88倍,多发生于胆囊切除术后10-15年<sup>[108]</sup>。由于胆囊切除术后这些因素的影响,近年来腹腔镜保留胆囊取石、息肉摘除术作为治疗胆囊结石、息肉等胆囊良性疾病的治疗方法之一,具有创伤小、恢复快、并发症少等特点,在临床上应用逐渐增多,但UGC与结石、息肉术后再复发逐渐成为胆囊保留取石或息肉摘除手术后不可避免的问题,成为制约胆囊保留性手术发展的重要因素,保留胆囊息肉摘除后息肉复发率0.1%,胆囊结石复发率为3.9%,UGC发生率为0.53%<sup>[109]</sup>。由于保胆手术中的胆囊切开、术中反复冲洗和挤压胆囊、术中胆道镜、腔内超声检查等方法的运用,将难以避免造成胆汁外溢,如果存在恶性肿瘤时有促进肿瘤腹腔转移的可能,恶变的胆囊息肉摘除术后可能存在基底部肿瘤残留。

因此,对于有胆囊结石或/和息肉的患者有强烈保胆治疗愿望时,应严格掌握保胆手术的指征,对于存在胆囊癌高危因素的胆囊良性疾病不宜采用保胆手术治疗,不应将患者主观保胆愿望作为保胆治疗的附加条件,严格掌握保胆手术的技术规范和适应证,术前需要影像学和血肿瘤标记物等严格筛查,加强术中对可疑胆囊壁病变或息肉快速病理检查,降低UGC发生率。

## 6 结论

UGC是在胆囊切除术中或术后意外发现的,由于UGC临床上常以胆囊结石、慢性胆囊炎表现为主,早期缺乏特异性临床表现、影像学特征和特异性血清肿瘤标志物,导致早期确诊困难,易误诊或漏诊。随着LC临床应用和手术指征不断扩大,UGC发生率逐渐增加,如何降低UGC发生率和处理好不同分期的UGC,是目前临床医生面临的主要问题,只有加强规范化的临床诊治流程,才能有效降低UGC发生率,提高临床疗效(图1)。虽然现在的影像学检查和血清肿瘤标志物虽然缺乏特异性,但这些辅助检查的异常表现能够为临床胆囊癌早期诊断提供重要的参考价值,尤其对于存在胆囊癌高危因素的患者,临床医生要引起足够的重视。与术前已确诊的胆囊癌相比,因为UGC仅行单纯胆囊切除,未按恶性肿瘤原则实施手术,而且不同病理分期临床处理具有相对特殊性,因此需要采用个体化的治疗方案,选择合适的治疗时机和方法,术后加强患者心理支持和其它辅助治疗,才能提高UGC疗效。

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