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述评 EDITORIAL

胆囊癌外科规范化治疗策略的探讨与思考

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Surgical treatment of gallbladder cancer: Strategy and optimization

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Abstract
Gallbladder cancer is the most common malignant tumor of the biliary tract. It is difficult to diagnose early due to the lack of special symptoms and physical signs. Most cases are diagnosed in advanced stages and the response to traditional chemotherapy and radiotherapy is extremely limited, with modest impact on overall survival. Despite improvements in outcome associated with extended resections, selection of patients for such extensive surgery remains controversial. In this article, we analyze and discuss the key issues about the surgical management of gallbladder cancer, with the hope of a more comprehensive recognition of this malignancy.

Key Words: Gallbladder cancer; Surgical treatment; R0 resection; Lymphadenectomy

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摘要
胆囊癌是胆道系统最常见的恶性肿瘤, 因其缺乏早期特异性症状和体征, 因此多数病例发现时已属中晚期, 且对放化疗不敏感, 总的预后较差. 根治性的胆囊癌切除术可延长患者的生存时间, 然而目前对于具体手术方式的选择尚存在一些争议. 本文就胆囊癌术式的合理规范化选择进行分析和探讨, 希望提高对于胆囊癌手术治疗的认识.

关键词: 胆囊癌; 外科治疗; R0切除; 淋巴清扫

核心提示: 胆囊癌术式的选择应该根据临床病理分期进行, 不同病理分期结合患者的一般情况而选择不同的术式. 如不能决定术式与切除范围, 则术中快速冰冻病理检查以确定切缘和引流淋巴结阳性与否应该成为判断的依据.

背景资料
胆囊癌是消化系恶性程度很高的肿瘤, 因其缺乏早期特异性临床症状和体征, 多数病例发现时已属晚期. 目前手术是可能治愈的唯一方式, 提高手术治疗效果, 改善患者预后的关键在于选择规范合理的手术方式. 而目前临床对于胆囊癌术式的认识和实施尚不统一, 部分分期术式的选择还存在很多争议.

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研发前沿
胆囊癌的手术方式主要是根据不同临床病理分期进行选择的. 而每个分期具体的术式选择又存在一些争议. 选择扩大切除范围以达到肿瘤的根治性切除还是缩小切除范围以减少手术创伤是目前争议的焦点. 如何保证在肿瘤根治性切除的前提下尽量减少手术创伤是研究的热点问题.

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0 引言

胆囊癌是胆道系统最常见的恶性肿瘤, 约占整个胆道系统肿瘤的80%-95%[1,2]. 其发病率约为0.8%-1.2%, 位居消化系第5位[3]. 日本、韩国、印度、巴基斯坦、智利等国家和地区发病率较高[1]. 由于早期胆囊癌缺乏特异性临床症状和体征, 并且肿瘤恶性程度高、侵袭性强, 加之胆囊特殊的解剖位置, 容易侵犯肝脏等周围组织, 所以多数病例发现时已经较晚[4], 大多数有症状的患者手术不能完整切除肿瘤[5]. 只有约10%的患者确诊时还能进行手术治疗[6], 约50%的病例发现时已经出现了转移[6,7]. 胆囊癌患者总的预后较差. 意外胆囊癌中位生存期平均有26.5 mo, 而术前确诊或者怀疑的患者则只有9.2 mo[8]. 胆囊癌患者5年总的生存率仅仅只有5%[1,9]. 提高胆囊癌患者生存期、改善预后的关键在于早期诊断、早期手术以及选择合理规范的手术方式, 而目前临床对于胆囊癌术式的认识和实施尚不统一, 部分分期术式的选择还存在很多争议, 因此对于胆囊癌手术方式的规范选择需要一个重新的探讨和认识.

1 胆囊癌外科治疗术式的选择

由于目前缺乏有效的辅助放化疗手段, 手术切除肿瘤仍旧是胆囊癌最有效的治疗手段[10,11]. 手术方式主要包括单纯胆囊切除术、胆囊癌根治性切除术、胆囊癌扩大根治术及姑息性手术等. 胆囊癌不同临床分期外科治疗术式的选择如图1所示. 有报道达到R0切除的胆囊癌患者总的5年生存率为21%-69%, 而未达到R0切除的患者则几乎为0[12]. 因此手术治疗的目的是能够达到肿瘤完整切除, 获得阴性切缘, 即达到R0切除[13]. 然而研究[14]表明即使是扩大根治术, 也只有43%的患者能够获得这个效果.

1.1 Tis和T1a期的手术选择 原位癌(Tis)和T1a期的胆囊癌肿瘤仅局限于黏膜层和固有层, 通常认为此类患者通过单纯胆囊切除术即可达到根治的目的[15,16], 更进一步的手术不能更好的改善预后反而增加了手术的创伤[17,18]. 此外有研究[19,20]表明Tis和T1a期患者淋巴结转移率不超过2.5%, 因此也不建议行淋巴结清扫. 有报道[18]Tis和T1a期胆囊癌患者行单纯胆囊切除术可以达到外科治愈, 其5年生存率为100%. Shirai等[21]对比了行单纯胆囊切除术和根治性切除术的T1期患者, 发现预后没有差别, 因此认为不需要再行任何进一步外科治疗. 然而Tis和T1a期患者占所有胆囊癌患者的比例不超过10%[10,22].

1.2 T1b期的手术选择 T1b期肿瘤侵及胆囊肌层, 对此类患者行单纯胆囊切除术还是根治性胆囊切除术尚存在一些争议. Bach等[23]一项包含39例的研究报道了T1期胆囊癌的患者经过单纯胆囊切除术治疗后, 5年生存率可以达到100%[10,22]. Wakai等[17]报道了T1b期患者行单纯胆囊切除术10年生存率为87%. 同样日本学者一项包含了498例患者的回顾性研究发现, T1a和T1b期5年生存率分别为99%和95%, 单纯胆囊切除术和根治性切除术对于改善T1期患者生存率差异无统计学意义[24]. 然而也有学者[25,26]认为T1b期中约有3%-28%的患者出现阳性淋巴结, 如果仅仅行单纯胆囊切除术, 有导致局部再发的可能. Pawlik等[27]对115例接受单纯胆囊切除术患者的术后病理分析研究显示, 46%的患者肿瘤切缘呈现阳性. 另有报道[18,28]行单纯胆囊切除术的T1b期患者有15%-20%的存在隐性淋巴结转移, 有10%的存在胆囊床肿瘤残余. You等[29]的报道指出有3.8%的患者出现了淋巴结转移, 1.9%的患者出现了淋巴管浸润, 对这部分患者实施根治性胆囊切除术, 其5年生存率可以达到96%. Lee等[30]对141例T1b期患者研究发现, 肝脏部分切除和淋巴结清扫并没有显示更好的预后结果, 但是阳性切缘和淋巴结转移却预示着很差的预后. 另有研究[31]显示根治性胆囊切除术和单纯胆囊切除术的生存率差异无统计学意义, 然而根治性胆囊切除术患者的复发率只有7%, 而单纯胆囊切除术的复发率却升高到了17%. 因此, T1b期患者手术治疗争议的焦点在于单纯胆囊切除术能否保证R0切除. 我们认为可以术中对肿瘤切缘与局部淋巴结施行快速冰冻病理检查, 对于明确的没有淋巴转移和切缘阴性的T1b期患者, 实施单纯胆囊切除术即可, 而对于确定的或者高度怀疑的有切缘阳性或淋巴转移的T1b患者, 行胆囊根治性切除术对于患者远期复发率的降低有明显改善. 我国学者报道了术中快速冰冻病理检查的灵敏度和特异度分别为83.3%

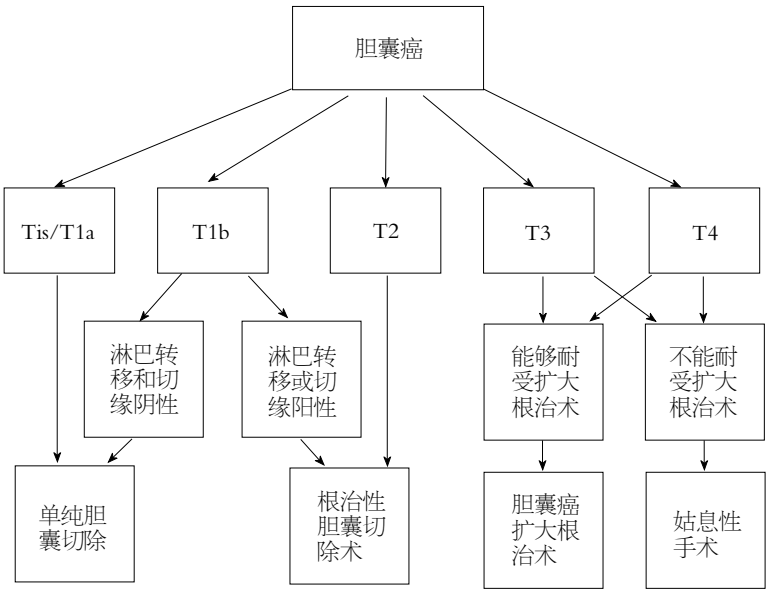

图 1　胆囊癌外科治疗术式的选择.

相关报道
为了保证在肿瘤根治性切除的前提下尽量减少手术损伤, 已有文献提出可以施行术中快速冰冻病理检查来确定肿瘤切缘和引流淋巴结阳性与否, 从而决定是否进一步扩大手术切除范围. 并且有报道术中快速冰冻病理检查效果良好.

和100%[32].

1.3 T2期的手术选择 T2期胆囊癌侵及肌层及周围结缔组织, 而没有扩大到超出浆膜和侵犯肝脏, 但由于胆囊和肝脏连接的部分没有浆膜层[33], 即使T2期肿瘤确认局限于胆囊壁内, 单纯的胆囊切除也不能到达根治性切除的目的[20]. 很多研究[34-36]已经报道了包含部分肝脏切除的根治性胆囊切除术对于提高T2期胆囊癌患者的生存期有重要意义. 有学者研究[37]发现T2期患者行单纯胆囊切除术切缘阳性率高达24%, 淋巴结转移率高达39%-54%[38,39]. 对于T2期胆囊癌患者, 根治性胆囊切除术可以明显提高5年生存率[24,40]. Shindoh等[41]一项包含252例T2期患者, 平均随访时间为58.9 mo的研究显示, 相比于单纯胆囊切除术, 根治性切除术减少了51%的死亡风险. Chijiiwa等[40]发现T2期胆囊癌患者单纯胆囊切除术5年生存率仅仅只有17%, 而根治性切除术则提高到了59%. 另有学者[23,42]报道了T2期单纯胆囊切除术和根治性胆囊切除术的5年存活率分别为40%和90%. 这些数据表明, 胆囊根治性切除术治疗T2期患者其复发率显著低于单纯胆囊切除术, 而生存率则明显高于单纯胆囊切除术, 因此T2期患者一般建议行胆囊根治性切除术.

胆囊根治性切除术是指切除胆囊床肝脏Ⅳ和Ⅴ段边缘至少2 cm, 并且进行N1站的淋巴结清扫. 与T1期相比, T2期淋巴结转移率明显升高, 5年生存率明显降低, 因此更加要强调T2期的区域淋巴结清扫. T2期患者的淋巴结清扫包括门静脉、肝动脉和肝门旁淋巴以及周围组织. 甚至有学者[43]认为应该对T2期淋巴的清扫更加彻底, 除了上面提及的淋巴结外, 他们还提议胰头后方、十二指肠部分淋巴结及腹腔干淋巴结的清扫. Bartlett等[44]对T2期的患者实行胆囊床肝脏Ⅳb和Ⅴ段切除, 在清扫N1站淋巴结的同时清扫了了N2站淋巴结, 结果显示, 患者3年生存率可以到达90%-100%. 然而, 对于胆囊床肝脏的切除范围尚存在一些争议. 有学者主张切除范围应该达到至少30 mm[9], 因为部分胆囊的静脉直接引流入肝脏的胆囊床, 有1/4的T2期患者显微镜下可见胆囊癌肿瘤侵袭肝脏边缘的深度达2.5 cm[45], 对于这些患者肝脏胆囊床切除范围必须超过25 mm才能达到R0切除. 而Yoshikawa等[46]对201例患者的回顾性研究发现, 胆囊床肝段的切除只有对肿瘤侵袭肝脏超过20 mm深度的患者预后有改善. 另有学者[47]提出对于肿瘤位于肝脏面, 侵袭到胆囊床或者胆囊颈的T2期患者应该行肝脏部分切除术, 而对于肿瘤位于腹膜侧的患者, 肝脏部分切除不是必须的. 这些研究也提示我们, 可以根据术中胆囊床肝脏切缘的冰冻病理检查结果来进行切除范围的选择, 直至达到阴性切缘, R0切除.

1.4 T3期的手术选择 T3期的胆囊癌肿瘤已经穿透浆膜, 可能直接侵袭临近的器官组织, 如肝脏、十二指肠、胰腺等, 这种情况下需要更加彻底的切除, 除行右半肝及尾状叶(如果有)切除外[18], 还需行区域淋巴结清扫及其他可能

创新盘点
文章分析比较了近年来胆囊癌不同临床分期不同术式治疗的优劣, 并探讨总结了具体分期最佳的术式选择, 提出术中快速冰冻病理检查应该成为手术切除范围判断的依据.

受侵袭的组织的清除[48]. 甚至有学者[18,48]提出施行临近器官组织切除, 包括行胰十二指肠切除术以提高预后. Cubertafond等[49]研究显示T3期患者平均生存期为8 mo, 中位生存期为6 mo. 日本学者对T3期患者行扩大根治术, 5年生存率为44%[50]. 同样Kondo等[51]也报道了对晚期胆囊癌行胰十二指肠切除术的R0切除, 5年生存率可以达到52.7%. 这些研究表明胆囊癌扩大根治术对于提高T3期患者的生存率是有一定意义的. 然而也有学者认为胆囊扩大根治术的主要困难并不在于肿瘤局部侵犯器官的切除难度, 而是在于受累淋巴结清扫的彻底性, 即使将肿瘤完整切除, 做到切缘阴性, 也不能确定无远处淋巴结转移. 而这些扩大根治手术局部创伤大、并发症多、死亡率高, 预后改善作用有限, 对于手术适应证的选择还需商榷[52,53].

1.5 T4期的手术选择 有学者[54]认为T4期的胆囊癌已经出现广泛的门静脉和肝动脉侵袭以及远处转移, 此时行手术治疗已经不能完整切除肿瘤了. Cubertafond等[49]报道了T4期患者中位生存期和平均生存期仅为2 mo和3 mo. 然而有研究[35,55]显示随着外科技术及麻醉水平的提高, 对T3和T4期患者行更加广泛的外科切除是安全的, 并且有一个不错的长期生存率. 日本一项研究[56]报道了对T3和T4期患者行非解剖性肝切除或者胰十二指肠切除术后, 患者5年生存率可以达到50%, 中位生存期为58.5 mo. 另有学者[57]对比了肝胰十二指肠切除术和非手术患者的预后, 结果显示, 肝胰十二指肠切除术患者1年和2年生存率分别为57.0%和28.6%, 而非手术治疗患者1年生存率仅仅只有5.8%, 中位生存期只有2 mo. 这说明积极地手术干预对于改善T4期患者的预后可能有一定实际意义.

一般认为T4期中已经发生远处转移的患者极少有根治性切除的可能, 而在复发的患者中, 再切除达到根治的机会也很少[58]. 此时应以姑息治疗, 改善患者生活质量为主, 如单纯胆囊切除减少血管组织压迫、胆肠胃肠吻合保持腔道通畅等. Donohue等[59]发现尽管根治性切除术对于个别患者可能有积极的作用, 但是对于提高总的5年生存率没有明显意义(根治性手术与单纯胆囊切除术5年生存率分别为33%和32%). 我国学者一项包含60例N2站淋巴结转移的进展期胆囊癌病例的回顾性研究[60]显示, 扩大的淋巴结清扫相对于区域淋巴结切除并没有改善患者的预后, 反而增加了病残率和死亡率, 因此不建议有N2站淋巴结转移的进展期胆囊癌行扩大的淋巴结清扫术. 然而, 也有学者研究[61]提示T4N0期患者经过积极手术治疗可以长期存活. 甚至在年纪超过70岁的患者, 经过手术治疗也可以延长生存期[44,62]. 这些研究表明随着外科技术的不断改进、麻醉水平的提高及监护条件的改善, 手术并发症及死亡率逐渐降低, 对于那些能够耐受手术的患者, 扩大根治术可能会改善晚期患者的预后.

2 腹腔镜手术与传统开腹手术

由于胆囊癌隐匿的高侵袭性, 而腹腔镜检查可以发现大约有39%-48%的患者不适合手术[63,64], 因此有学者建议腹腔镜相比于开腹手术应该成为一种优先的常规检查, 一旦在腔镜下发现转移, 那么组织活检可以避免非治疗性的剖腹手术[65].

Rakić等[12]认为对于术前怀疑或者已经明确是胆囊恶性疾病的患者施行腹腔镜胆囊切除术(laparoscopic cholecystectomy, LC)是胆囊癌治疗的绝对禁忌证. 研究[8,24]发现约20%的胆囊癌患者在行腹腔镜手术时会发生胆囊破裂, 这些发生术中胆囊破裂的患者生存率明显低于那些术中胆囊未破裂的患者. 因为腹腔镜相对于开腹手术容易导致肿瘤的腹腔播散和取出胆囊的腹壁穿刺点的种植转移, 因此有学者提出对于胆囊癌患者腹腔镜穿刺点应该行腹壁全层切除[40,66]. 有报道[67]术中胆囊穿孔相比于胆囊未穿孔的患者, 腹壁穿刺点的种植转移率从9%增加到了40%. 另有研究[18]显示LC的意外胆囊癌患者中, 穿刺点种植转移率高达17%. 并且CO_2形成的气腹也可能会促进肿瘤的播散[68]. 但是也有学者研究[69]发现腹腔镜手术腹壁种植转移的发生率并没有提高. Gourgiotis等[9]对8例患者术中使用保护性回收袋, 结果发现这一措施并没有阻止穿刺部位的种植转移. 有研究[70]也报道了LC相比传统开腹手术并没有明确不利的影响, 术中更加小心地取出胆囊, 防止胆囊破裂及胆汁溢出可以降低腹壁穿刺部位的种植转移率[71,72]. 对于Tis、T1a和T1b期患者, 实施LC手术5年生存率也可达到85%-100%, 与传统开腹手术差异无统计学意义[32], 而众所周知LC在减少手术创伤、减

短恢复时间等方面具有明显的传统开腹手术无可匹敌的优势. 并且已有学者[73]在更为复杂的条件下行腹腔镜胆囊癌扩大根治术, 效果也良好. 因此, 不必将腹腔镜手术刻意排除在胆囊癌治疗方法的大门外.

3 意外胆囊癌的手术治疗

意外胆囊癌通常是指术前检查未能发现, 而在术中或者术后依靠病理检查结果证实的胆囊癌[74,75]. 文献报道[76]只有30%左右的胆囊癌是术前发现的, 而70%-75%的胆囊癌属于意外胆囊癌[77]. 有研究[15,78]显示意外胆囊癌的发病率为0.19%-2.8.0%, 此类患者大多数临床分期为T1和T2期[28,79]. 再次手术行根治性切除是T2和T3期胆囊癌患者获得长期生存的唯一机会[80], 因此有学者提出意外胆囊癌病理证实为T2、T3分期的患者, 需再次手术行根治性切除, 避免肿瘤残余[81]. 手术方式包括非解剖性肝切除(胆囊床切除, 即Ⅳb和Ⅴ段切除), 或者是标准的解剖性肝切除, 如右半肝切除术. 具体局部切除和淋巴结清扫范围需根据术中探查、肿瘤切缘阳性与否来判断.

4 结论

尽管在过去的几十年里, 手术技术取得了长足的进步, 然而进展期胆囊癌患者的治疗进展却很小[5,82]. 早期诊断、早期治疗、选择规范合理的手术方式, 在达到R0切除的前提下尽可能地减少手术损伤是提高胆囊癌生存率的关键. Tis和T1期患者所占比例极少, 而T4期患者无论手术与否预后都较差, 因此我们要重视对胆囊癌中T2和T3期的患者行根治性手术以提高术后存活率. 对于部分分期肿瘤的切除和淋巴结清扫范围不能确定的病例, 术中快速冰冻病理检查以确定切缘阴性和淋巴清扫干净与否意义非凡, 毕竟我们目前所使用的临床分期主要都是根据肿瘤侵袭深度和淋巴结转移状况来判断的.

应用要点

对手术切缘和引流淋巴结行术中快速冰冻病理检查, 如切缘与淋巴结均为阴性, 则可不必扩大手术范围; 如切缘或淋巴结阳性, 则应扩大切除范围直至切缘和淋巴结阴性. 这样既能达到肿瘤的根治性切除, 又能最大程度的减少手术创伤.

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名词解释

R0切除: 指手术完整根治性切除肿瘤, 获得大体或者显微镜下阴性切缘;

意外胆囊癌: 指术前临床检查未能发现, 诊断为胆囊良性疾病而行胆囊切除术, 在术中或术后经病理检查而确诊的胆囊癌.

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同行评价

胆囊癌是胆道系统常见的恶性肿瘤, 近年来在我国有明显增加趋势. 由于其恶性度极高, 危害极大. 本文就胆囊癌术式的合理规范化选择进行了综述分析, 对于提高胆囊癌手术治疗的认识具有一定的指导意义.

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