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经皮肝穿刺胆道引流/胆道支架植入术治疗肝外胆管癌合并梗阻性黄疸的研究进展

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Percutaneous transhepatic cholangial drainage/percutaneous transhepatic biliary stent implantation for treatment of extrahepatic cholangiocarcinoma with obstructive jaundice

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Abstract

Extrahepatic cholangiocarcinoma is a malignant tumor originating from the extrahepatic bile duct including the

hilar region to the lower bile duct of the common bile duct. With the development of interventional techniques and medical materials, percutaneous transhepatic cholangial drainage (PTCD) or percutaneous transhepatic biliary stent implantation (PTBS) has become the main treatment to relieve biliary obstruction. However, the occurrence of postoperative complications seriously affects the prognosis of patients, and the combination of biliary stenting with local treatment has been found to significantly prolong the time to biliary patency. This article reviews the progress of PTCD/PTBS in the treatment of extrahepatic cholangiocarcinoma with obstructive jaundice, evaluates its clinical efficacy, and points out the current problems and possible solutions to provide more reference for subsequent related studies.

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Key Words: Extrahepatic cholangiocarcinoma; Obstructive jaundice; Percutaneous transhepatic cholangial drainage; Percutaneous transhepatic biliary stent; Complications; Combined local therapy

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摘要

肝外胆管癌(extrahepatic cholangiocarcinoma, ECC)是起源于肝外胆管包括肝门区至胆总管下端胆管的恶性肿瘤, 确诊时胆道受侵犯压迫常合并出现梗阻性黄疸, 患者多处于中晚期而丧失根治性切除机会。随着

介入技术及医学材料的发展, 经皮肝穿刺胆道引流术(percutaneous transhepatic cholangial drainage, PTCD)或胆道支架植入术(percutaneous transhepatic biliary stent, PTBS)已成为解除胆道梗阻的主要治疗方法。然而, 术后并发症的发生严重影响患者的预后, 目前发现胆道支架联合局部治疗可显著延长胆道通畅时间。本文综述关于PTCD/PTBS治疗肝外胆管癌合并梗阻性黄疸的进展, 评价其临床疗效, 并指出目前存在的问题及处理方法, 为后续相关研究提供更多参考。

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关键词: 肝外胆管癌; 梗阻性黄疸; 经皮肝穿刺胆道引流术; 经皮肝穿刺胆道支架植入术; 并发症; 联合局部治疗

核心提要: 经皮肝穿刺胆道引流/胆道支架植入术(percutaneous transhepatic cholangial drainage/percutaneous transhepatic biliary stent, PTCD/PTBS)是目前治疗肝外胆管癌合并梗阻性黄疸的有效介入治疗方法, 为进一步提高患者生存率及生活质量, 本文综述防治相关并发症及PTCD/PTBS联合局部治疗的进展。

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0 引言

胆管癌是起源于胆管上皮的恶性肿瘤, 占消化系统恶性肿瘤的3%^[1]。根据发生部位分为肝内胆管癌和肝外胆管癌, 肝外胆管癌又进一步分为肝门部胆管癌和远端胆管癌^[2]。梗阻性黄疸是指由恶性肿瘤本身阻塞、压迫或淋巴结转移肿大压迫胆道, 导致不同部位胆道狭窄闭塞引起的梗阻性病变, 引起的全身皮肤、黏膜及巩膜黄染。随着胆管梗阻进行性加重, 胆汁大量淤积, 胆红素释放入血引起高胆红素血症, 患者出现感染、肝肾功能及心功能等多脏器损害, 预后极差^[3-5]。恶性梗阻性黄疸起病隐匿, 大多数患者发现已为中晚期, 无法行根治手术, 经皮肝穿刺胆道引流/胆道支架植入术(percutaneous transhepatic cholangial drainage/percutaneous transhepatic biliary stent, PTCD/PTBS)为目前治疗恶性胆道梗阻的主要方法^[6]。但随着PTCD/PTBS的广泛应用, 胆道感染、胆道出血、胆漏、急性胰腺炎、支架再狭窄、引流管移位、脱落及阻塞等并发症很常见, 严重影响患者预后^[7]。因此, 胆道支架联合¹²⁵I粒子放射疗法、动脉灌注化疗或化疗栓塞(hepatic artery infusion chemotherapy/transcatheter

arterial chemoembolization, HAIC/TACE)、射频消融(radiofrequency ablation, RFA)、不可逆穿孔(irreversible electroporation, IRE)以及光动力疗法(photodynamic therapy, PDT)等联合局部治疗方法可提高患者生活质量及生存期, 将成为今后探索的方向。本文就近年来国内外关于PTCD/PTBS治疗肝外胆管癌合并恶性胆道梗阻的相关研究进行综述。

1 临床疗效及应用价值

1.1 临床疗效 PTCD/PTBS是一种有效治疗恶性梗阻性黄疸的介入治疗方法, 通过形成胆汁的外引流或穿越狭窄部位位置管形成胆汁的内外引流, 有效降低胆道压力。有学者^[8]评估PTCD/PTBS姑息治疗恶性梗阻性黄疸患者的疗效, 术后生化指标显著下降, 肝功能明显改善, 梗阻性黄疸相关瘙痒消退。与Duan的研究结果一致^[9]。Pranculis等^[10]研究经PTBS治疗的222例恶性胆道梗阻患者, 术后平均生存时间为143.3 d±20.6 d, 中位生存期为74 d±10.2 d, 术后(1、3、6、12) mo的总生存率分别为81.7%、47.3%、29.6%、10.4%, 其中诊断为胆管癌合并梗阻性黄疸的患者存活时间最长(191.7 d±46.4 d), 证实了PTCD/PTBS不仅可以改善患者的临床症状, 同时提高患者生活质量并延长生存期。

PTCD长期体外引流易导致电解质和酸碱平衡紊乱, 经PTBS是其延续治疗, 可通过置入支架的自膨胀特性, 使胆管的狭窄梗阻部位恢复通畅, 从而恢复胆汁正常的内引流及生理功能, 可延长患者胆道通畅时间及生存期, 并为后续综合治疗提供额外的生存获益^[11,12]。

1.2 对手术切除的价值 目前手术切除仍是肝外胆管癌的首要治疗方法, 但胆道梗阻引发的术前高胆红素血症会增加手术的风险^[13]。因此, 行术前胆道减压是可行的, PTCD/PTBS可及时有效地解除胆道梗阻, 降低术后肝衰竭的风险, 使患者获得进一步手术治疗的机会^[14]。有研究比较术前胆道引流和直接手术对恶性梗阻性黄疸患者的疗效, 结果发现术前引流组的术后并发症总体发生率较低^[15]。最近一项研究得出相同的结论^[16], 提示接受术前胆道引流治疗的远端胆管癌的手术结局得到改善。但关于肝门胆管癌是否应行术前减黄仍争议不断^[17], 提示PTCD可能增加胆管炎、胰腺炎等并发症的发生率, 不能明确改善患者的主要预后。

2 术后相关并发症及防治

2.1 胆道感染 胆道感染是PTCD/PTBS术后最常见和不容忽视的并发症, 主要表现为寒战高热, 血白细胞异常增多, 胆汁细菌培养阳性等。多由于胆汁淤积或术中造影剂应用过多或反复应用易使感染胆汁入血; 当胆汁经

PTCD外引流破坏水电解质平衡,抵抗力下降,也进一步增加了细菌逆行性感染的概率,主要发病机制包括细菌从小肠上行,以及细菌穿过小肠壁迁移后经血行传播至门静脉血^[18]。因此,术前必要时行胆汁培养+药敏试验,选择敏感抗生素。术中操作者注意动作轻柔,避免胆道造影时压力过大,时刻遵守严格的无菌原则。术后胆道保持引流通畅,PTCD外引流管定期对胆道进行冲洗,在支架植入术后尽早拔出外引流管,以降低胆道感染的风险。

有研究显示^[19],PTCD外引流组感染率为9.4%,而PTBS组为28%,PTBS组的感染率高于PTCD组可能与支架植入过程中导丝将细菌带入胆道有关,此时细菌逆行进入胆道的机会也在增加,结果与传统观点一致,认为支架越过十二指肠乳头会导致壶腹括约肌收缩功能障碍,抑制防反流功能,造成胆肠反流,肠道细菌进入胆道系统,细菌滋生引发胆道感染。但Li等^[20]报道术后早期胆道感染发生率在支架跨过十二指肠乳头组(7.1%)明显低于支架未跨过十二指肠乳头组(20.3%)。随后的研究提出梗阻部位若超过十二指肠乳头3 cm时,选择支架跨过十二指肠乳头可降低胆道感染率^[21]。

2.2 胆道出血 胆道出血多与肝凝血功能障碍或术中穿刺针误入血管等医源性操作有关,主要为术后引流出血性胆汁,右上腹痛,消化道出血,严重时出现休克等。胆道出血作为有生命威胁的出血性疾病,明确出血部位并及时有效的止血治疗很关键。自身凝血障碍者则给予止血、保肝等对症治疗好转。一般介入造影可明确出血部位,同时可施行栓塞止血等治疗,而胆道大出血者则需尽快输注红细胞或经导管动脉栓塞术^[22]。目前有较多研究发现,超声引导下PTCD术可清晰显示肝内、外胆管走行和扩张程度,选择最佳的穿刺路径,避开肝内大血管,明显降低胆道出血等并发症的发生率^[23,24]。但此操作需医院配备较好的仪器及水平较高的超声医师。

2.3 胆漏 胆漏是较为严重的并发症,主要原因是术中损伤胆管或引流管放置不当,以及术后引流管脱落所致。临床表现为右上腹或全腹压痛、反跳痛等腹膜刺激征,胆汁引流量减少。一般不需要特殊处理,可密切观察。对于腹膜炎症状严重者,积极寻找并处理病因后,腹腔积液可以给予充分引流。报道称大多数胆漏通过胆道系统减压消退,胆道系统减压通常经皮或经内镜逆行胰胆管造影可明确治疗,准确率接近100%,79%-85%的病例可确定胆漏的确切位置^[25]。一般PTCD/PTBS术后出现胆漏主要是穿刺点引流管口漏,经过缝合管口或者更换导管型号后胆漏好转,放置引流管时,注意引流管直径与扩张管直径相匹配。若造影发现PTCD管部分滑脱时,可在透视下经导引钢丝重新置管^[26]。

2.4 急性胰腺炎 PTCD/PTBS术后并发急性胰腺炎的发生率较低,但它的发生会严重威胁患者预后,应予重视和预防,主要表现为术后上腹部持续疼痛,发热,血尿淀粉酶升高,予以禁食、抗炎、补液、维持电解质平衡等治疗后病情缓解。学者认为对于壶腹部的肿瘤,应尽量减少应用导管及导丝在壶腹部操作,尽可能避免在胰管内注入大量对比剂,以免发生胰腺炎^[27]。与经内镜逆行胰胆管造影术相比,经PTCD/PTBS引起胰腺炎的风险较小,若行内外引流发生胰腺炎,可将内外引流改为外引流。关于并发急性胰腺炎的研究中最常见原因是反复插管损伤乳头及括约肌,插管困难为高危因素,随着插管时间的延长,发生胰腺炎的风险增加^[28,29]。

2.5 支架再狭窄 PTCD/PTBS主要治疗作用是改善梗阻症状,而对形成其梗阻病因的恶性肿瘤本身并无治疗作用,随着疾病的发展,置入的支架终将会堵塞引起再次狭窄^[30]。支架再狭窄是支架植入后影响患者生存期最常见的远期并发症,狭窄后又出现梗阻性黄疸等一系列症状,此时患者一般情况差,再治疗及预后往往不甚理想^[31]。一般认为再狭窄的原因有:(1)肿瘤生长(主要);(2)肉芽组织增生及胆管瘢痕形成;(3)胆汁淤积以及胆泥形成;(4)血凝块或食物残渣阻塞等。夏兴阳等^[32]收治因肝门部胆管癌所致的胆道高位梗阻患者而行胆道支架植入术,对术后出现再梗阻行胆道外引流术的36例病例进行分析,发现本组有25例(69.4%)因肿瘤生长导致支架再狭窄,7例为急性胆管炎所致,4例为胆道泥沙堵塞支架。解决后再狭窄最常用的办法是再次植入胆道支架,目前改变胆道的支架构造也广泛应用于临床,认为自膨式金属裸支架(self-expanding metallic mesh stent, SEMS)相对于塑料支架可明显提高支架通畅率,降低并发症发生率^[33]。近几年的研究中发现胆道支架合其他抗肿瘤治疗方法更能显著提高胆道通畅率,而抑制肿瘤生长是解决问题的关键^[34]。

2.6 引流管移位、脱落及阻塞 PTCD术后引流管堵塞及脱落多由于引流管径较细、位置不佳或护理不佳等,会再次引起胆道梗阻,必要时可以通过造影调整导管位置避免并发症的发生影响患者预后。有学者^[35]回顾性分析超声引导下PTCD行胆汁引流解除胆道梗阻中,应用的引流导管内有猪尾装置,不易脱出,引流胆汁成功率明显提高;另外术中采取胆管引流管与引流袋之间增加一段约20 cm的无菌胶皮管,当胆汁引流不通畅时,通过向远端滑动挤压此段胶皮管给予引流管负压吸引,能保持引流管通畅,取得满意的效果。此外,笔者认为术中需谨慎选择穿刺点以及工具,并在术后护理中给予密切观察,避免出现引流管脱落或移位。

2.7 其他并发症 其他如胆心反射及肾衰竭等并发症

较少见。李建新等^[36]分析277例恶性梗阻性黄疸患者行PTCD/PTBS术, 有2例(3.51%)患者发生胆心反射, 主要表现为胆道操作过程中突发心率减慢、血压下降、胸闷气促以及心律失常等, 应立即采取阿托品静脉推注、补液以及对症处理, 待病情平稳后再行手术; 有2例(3.51%)出现肾衰竭, 表现主要是少尿, 重者为无尿, 肾功能检查提示血肌酐及尿素氮上升显著, 临床治疗多为补液、平衡电解质、增加血容量以及给予利尿剂, 重者可采取血液透析治疗。

3 胆道支架联合局部治疗

3.1 支架联合腔内近距离放疗(¹²⁵I粒子) ¹²⁵I放射性粒子通过持续性、小剂量、短程释放γ射线诱导细胞凋亡、抑制细胞增殖的原理, 从而控制胆道肿瘤生长, 延长胆道支架通畅时间及生存期^[37]。有学者研究^[38]胆管癌合并梗阻性黄疸患者, 一半接受胆道支架联合¹²⁵I链植入(研究组), 一半接受胆道支架植入(对照组), 发现研究组支架通畅时间中位数为41.71 wk±3.46 wk, 对照组为29.00 wk±5.81 wk。另一研究^[39], 同样比较恶性梗阻性黄疸患者中, 分别接受胆道支架联合¹²⁵I链植入(研究组)和胆道支架植入(对照组)的疗效, 研究组(10.0 mo±1.6 mo)术后支架通畅时间明显多于对照组(5.2 mo±0.4 mo), 进一步证明了胆道支架联合近距离放射治疗是更安全有效的。但患者接受率低, 且有许多问题待解决, 如粒子活度的选择、并发症、安全性等。

3.2 支架联合经血管途径治疗HAIC/TACE HAIC/TACE可抑制胆道肿瘤生长, 解决引起胆道梗阻性黄疸发生的主要原因, 延长患者的生存时间。TACE是通过导管向肿瘤注射栓塞剂和化疗药物, 通过栓塞肿瘤血管饿死肿瘤以及缓慢释放化疗药物杀灭肿瘤; HAIC是利用动脉化疗的原理直接插管到肿瘤的供血血管, 通过导管持续注射化疗药物杀灭肿瘤。有学者比较¹²⁵I与非¹²⁵I与TACE联合用于治疗伴有阻塞性黄疸不可切除的肝细胞癌患者, 联合组(6.000 mo±0.315 mo)较仅TACE组(4.000 mo±0.572 mo)有更多的胆道通畅时间^[40]。另一学者比较支架联合HAIC的同时加¹²⁵I(HAIC组)和支架联合HAIC(对照组)在恶性阻塞性黄疸的晚期胆管癌患者的疗效, HAIC组患者的生存期和支架通畅性明显优于对照组(中位生存时间: 362 d vs 185 d; 支架通畅的中位持续时间: 294 d vs 156 d)^[41]。现在部分经血管途径化疗联合其他综合治疗已取得小小成就, 未来将需要更多研究来验证这些结果。

3.3 支架联合胆道内消融(RFA/IRE) RFA通过热效应破坏肿瘤组织, 使肿瘤发生凝固性坏死, 减轻肿瘤负荷来控制疾病进展。Steel等^[42]首次对22例晚期胆道肿瘤

患者行RFA治疗, 术后并发症发生率低, 患者早期(30 d)及晚期(90 d)的胆管支架堵塞率均较低。有学者^[43]比较PTCD+RFA联合胆道支架植入术(研究组)和PTCD联合胆道支架植入术(对照组)治疗胆管癌合并梗阻性黄疸患者的疗效, 6 mo后, 研究组黄疸总发生率为11.67%, 低于对照组30.00%, 且研究组患者中位生存期和生存率均高于对照组, 证明了支架联合胆道内RFA疗效更显著。但由于该技术开展时间较短, RFA参数设置及临床远期疗效等需进一步证实。

IRE又称纳米刀, 是一种新兴的非热消融技术, 在影像引导下通过短脉冲高压电流破坏细胞膜导致细胞凋亡, 尤其适用于特殊部位实体恶性肿瘤, 避免损伤血管及胆道等肿瘤的周围结构^[44]。研究显示^[45], 恶性梗阻性患者肿瘤行IRE可安全地实现胆汁减压, 并允许长时间移除PTCD管, 术后患者症状减轻、生活质量改善, 且生存率有望提高。有学者进一步评估在不可切除的肝门胆管癌病例中行IRE联合术中胆道支架置入的安全性和有效性, 术后患者胆红素明显下降, 生存期显著延长^[46]。IRE几乎实现了完全肿瘤消融, 但IRE技术还需改进, 治疗过程中偶尔会出现心律失常、出血、手术后感染等症状^[47]。此外, 研究发现IRE消融术可能会留下完整的肿瘤抗原, 对重塑肿瘤微环境具有一定作用, 因此临床上考虑使用免疫刺激质粒进行局部根除和全身免疫治疗的结合, 目前IRE联合免疫治疗仍处于探索阶段^[48]。

3.4 胆道支架联合PDT PDT通过给患者静脉注射光敏剂, 光敏剂再分布在病理组织, 以适当波长的激光来启动活化过程, 产生光细胞毒性进而对目标组织造成选择性破坏, 临床上传统的光敏剂逐渐演变为具有聚集诱导发射效应的新一代光敏剂^[49]。Moole等^[50]比较胆道支架联合PDT和单纯胆道支架在恶性梗阻性患者的临床价值, 发现联合组的平均生存时间为413.04 d, 显著长于单纯支架植入组183.41 d, 表明PDT在保持胆道通畅及生存期方面具有重要优势。Chen等^[51]回顾性分析PTCD+PDT和仅PTCD在术后复发性肝外胆管癌的疗效, 术后联合组中位生存时间明显长于PTCD组(23 mo vs 10 mo), 提示PDT是一种创伤小、不良反应少的治疗方式, 值得临床进一步应用推广。但PDT技术操作复杂, 价格昂贵, 病人接受度较低, 中小型医院很难开展, 所以PDT的设备措施等有待探索。

4 结论

综上所述, PTCD/PTBS是治疗肝外胆管癌合并梗阻性黄疸的一种有效的介入治疗方法, 不仅有效减轻黄疸, 缓解临床症状, 尽早改善患者的肝功能, 延长生存期, 并为后续有可能获得根治性切除的患者获得进一步手术的

机会. PTC联合PTBS更能显著提高患者的生活质量. 同时, PTC/PTBS术后并发症严重影响治疗效果和预后, 为进一步提高胆道通畅率, 胆道支架联合局部治疗方案正在不断完善, 根据患者本身实际情况选择并制定个体化的治疗方案.

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• 消息 •

书 讯



本刊讯 由池肇春教授等主编的《代谢相关脂肪性肝病肝外并发症》已由天津科学技术出版社出版发行。

本书的出版为国内首创, 填补了国内有关这方面的空白, 拓宽了对《代谢相关脂肪性肝病》认识的高度和深度。《代谢相关脂肪性肝病肝外并发症》分总论和各论两部分。1-4章为总论, 分别介绍代谢相关脂肪性肝病肝外并发症研究现状与进展, 包括发病风险、发病机制和治疗近展; 脂肪代谢生物化学和分子生物学; 代谢相关脂肪性肝病肝外并发症免疫学; 肠道微生物生态失衡与代谢相关脂肪性肝病肝外并发症。5-18章为各论, 分别介绍代谢相关脂肪性肝病肝外并发症与机体各系统疾病的相关性。可为消化科、肝病科、内分泌代谢科、普外科、肿瘤科、影像科、其他相关科临床医师和从事MAFLD研究的人员学习和参考。

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