

超声内镜介入治疗在胆胰疾病中的应用

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[摘要] 超声内镜(endoscopic ultrasound, EUS)技术不仅在消化系统疾病诊断中得到长足发展,近年来随着内镜技术及配件设备的不断革新,超声内镜引导下的介入治疗也取得重要突破,尤其是在难治性胆胰疾病方面表现出突出优势。本文将结合最新的文献研究和工作经验,对EUS引导下的胆管引流术、胆囊引流术、胰管引流术、胰腺假性囊肿引流术、胰腺肿瘤治疗等相关介入治疗的最新进展进行阐述。

关键词: 超声内镜; 介入治疗; 引流; 胆管; 胰腺

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Application of endoscopic ultrasound interventional therapy in biliary and pancreatic diseases

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[Abstract] Endoscopic ultrasound (EUS) has been greatly developed in the diagnosis of digestive diseases. In recent years, with the continuous innovation of endoscopic technology and accessories, important breakthroughs have been made in endoscopic ultrasound-guided interventional therapy, especially in the treatment of refractory biliary and pancreatic diseases. Based on the latest literatures and work experience, in this paper, we reviewed the latest progress of EUS interventional treatment for biliary and pancreatic diseases, including EUS-guided bile duct drainage, EUS-guided gallbladder drainage, EUS-guided pancreatic duct drainage, EUS-guided-pancreatic pseudocyst drainage, and EUS-guided pancreatic tumor treatment.

Key words: Endoscopic ultrasound; Interventional therapy; Drainage; Biliary tract; Pancreas

内镜介入技术已广泛应用于胆胰系统疾病的治疗。借助胆管与胰管汇合进入十二指肠乳头的解剖结构,内镜逆行胰胆管造影术(endoscopic retrograde cholangio-pancreatography, ERCP)率先应用于胆总管结石、胆道梗阻、慢性胰腺炎等胆胰疾病的微创治疗。尽管ERCP的手术成功率不断提高,但仍有近5%的病例面临手术失败,如存在胆胰恶性肿瘤或消化道重建术后等高危因素。20世纪90年代初,线阵超声内镜(endoscopic ultrasound, EUS)的发展为EUS诊断和治疗带来了新的契机,随着专用设备及配件的不断改进,EUS引导下胆、胰管引流术逐渐成为ERCP失败时的首选替代方案,其比经皮引流方式更具可行性,且安全有效。此外,EUS对胰腺肿瘤性疾病、胰腺假性囊肿(pancreatic pseudocyst, PPC)、胆囊疾病等也确立了微创化的新型介入治疗

方案,并获得良好的临床效果。现就EUS在胆胰疾病介入治疗中的应用进行详细阐述,以指导临床选择合适的治疗方案,更好地促进技术的发展。

1 在胆道系统引流方面的应用

1.1 胆管引流术

EUS引导下胆管引流术(EUS-guided biliary drainage, EUS-BD)作为ERCP失败后的替代治疗已被广泛接受和应用^[1]。EUS-BD与经皮肝穿刺胆道引流术(percutaneous transhepatic cholangial drainage, PTCD)相比,成功率相似或更高而不良反应发生率更低^[2-3]。目前EUS-BD主要方法有肝胃吻合术(hepatico-gastrostomy, HGS)、胆总管十二指肠吻合术(choledochoduodenostomy, CDS)、辅助对接技术(rendezvous procedure, RV)、顺行支架置入术(antegrade stent, AS)和经肝顺行取石术(transhe-

patic antegrade stone removal, TASR)等。

1.1.1 EUS-HGS

EUS-HGS多数情况下用于十二指肠狭窄及解剖改变引起内镜无法到达十二指肠乳头时对肝门部梗阻进行姑息性胆汁引流治疗,有时亦可用于胆管远端梗阻及创建通往胆管的临时通道来解决胆道结石。荟萃分析报道EUS-HGS的技术操作成功率为96.6%,临床成功率91.3%^[4]。不良事件发生率15%~20%,常见的并发症包括气腹、胆漏、感染、出血和支架功能障碍^[5]。肝胃之间可放置塑料支架和覆膜自膨式金属支架(self-expandable metallic stent, SEMS)。覆膜SEMS有助于减少严重的不良事件,且方便再次干预^[6]。如通过覆膜SEMS在肝胃建立通道后,可以把十二指肠镜放入胃腔,通过十二指肠镜将超细胆管镜经支架进入肝内胆管,对肝内胆管结石、肿瘤等进行诊治。

1.1.2 EUS-CDS

EUS-CDS适用于实施ERCP失败以及进入十二指肠降部困难时远端胆管梗阻的引流治疗。相对EUS-HGS,EUS-CDS使用更广泛,因其穿刺路途相对较近且技术上容易,而临床效果相似。前述研究表明,EUS-CDS与EUS-HGS技术成功率和临床成功率接近,EUS-CDS技术成功率为95.0%,临床成功率93.1%,但与EUS-HGS相比,EUS-CDS手术时间稍短,不良事件发生率(12.2%)较低^[4]。SEMS在CDS手术方式中同样可获得较长的支架通畅时间^[7]。这两项技术的应用和远期效果与操作者相关,选用擅长的方式,效果好而不良事件少。

1.1.3 EUS-RV

如内镜可到达乳头位置但ERCP困难或失败时,EUS-RV比CDS和HGS更适用。穿刺可以经胃经肝途径或经十二指肠直接进入胆管,于十二指肠降部进行胆管穿刺成功率较高,时间较短^[8]。一篇荟萃分析报道EUS-RV总体成功率为84.4%,并发症发生率为15.6%。如EUS-RV经验丰富成熟,建议在行PTCD之前尝试EUS-RV^[9]。当然,随着技术的推广和成熟,EUS-RV操作的普及性及成功率会进一步提高。

1.1.4 EUS-AS

2010年,Nguyen-Tang等^[10]首次报道EUS-AS。EUS-AS主要用于解剖结构改变的不可切除远端恶性胆道梗阻病人,技术及临床成功率可达95%以上,不良事件发生率为11.4%~20%^[11-12]。EUS-AS经消化道操作,即使支架放置失败,亦可行HGS或CDS完

成内引流,而经皮途径失败后则只能留置外引流管,影响病人生活质量。另外,EUS-HGS与EUS-AS联合,支架通畅时间可能更长,不良事件发生率更低^[13],但需警惕胰管开口阻塞导致的急性胰腺炎。

1.1.5 EUS-TASR

EUS-TASR类似于EUS-AS技术,用于上消化道重建手术后胆管结石病人。据报道,EUS-TASR的成功率为60%~100%,不良事件发生率 $\leq 17\%$ ^[14-16]。随着相关临床工作的开展,这一技术有望替代耗时的气囊小肠镜ERCP。另一辅助取石技术为EUS引导的经胃ERCP(EUS-directed transgastric ERCP, EDGE),适用于消化道Roux-en-Y术后的胆管结石病人,利用双腔固定金属支架(lumen-apposing metal stent, LAMS)在胃和输出襻之间建立通道后行ERCP。EDGE治疗胆管结石,似乎比气囊小肠镜ERCP的成功率更高^[17],因为胃肠间建立通道后行ERCP操作与常规ERCP相似。但需注意胃肠道间的瘘口关闭问题。不能愈合的消化道瘘会造成严重危害。

1.2 胆囊引流术

EUS引导下胆囊引流术(endoscopic ultrasound guided gallbladder drainage, EUS-GBD)越来越受到内镜医师的青睐。与传统的经皮经肝胆囊引流术(percutaneous transhepatic gallbladder drainage, PTGBD)相比,EUS-GBD技术成功率和临床成功率相似,分别为EUS-GBD 96.5%比PTGBD 98.6%($P=0.05$),EUS-GBD 93.5%比PTGBD 91.9%($P=0.38$)^[18],其不良事件较少,再干预率较低^[19]。如有条件,使用前端带电烧灼功能的LAMS可提高安全性,减少胆囊炎复发和再入院^[18]。另外,EUS-GBD应用支架建立的通道也为内镜下保胆取石提供了可能,尤其是在LAMS问世以后。应用LAMS建立通道后,56%的病人结石可自行通过支架排除,进一步内镜取石后,高达88%的病人完全清除结石^[20]。因此,EUS-GBD可以作为PTGBD有效的替代方案,将来可能为更多的病人保留功能尚存的胆囊。

2 在胰腺疾病中的应用

2.1 胰管引流术

2002年,Bataille等^[21]首次描述EUS引导下胰管引流术(EUS-guided pancreatic duct drainage, EUS-PD)。随后这项技术逐渐在临床开展应用^[22]。EUS-PD主要适用于ERCP失败或不能行ERCP(如消化

道结构改变)的胰管梗阻病人。胰管梗阻的病因较多,包括慢性胰腺炎、胰头恶性肿瘤、胰肠吻合口狭窄、胰管离断综合征等。其中,胰腺良性疾病导致的胰管梗阻需胰管引流者更常见。Tyberg等^[23]对80例ERCP失败的病人实施EUS-PD,其中只有6例(8%)恶性胰管狭窄。EUS-PD存在两种不同形式,即EUS辅助对接内镜逆行胰管造影(EUS- rendezvous endoscopic retrograde pancreatography, EUS-RV-ERP)和EUS透壁引流(EUS-transmural drainage, EUS-TMD)。EUS-RV-ERP是利用穿刺针进入胰管后将导丝顺行穿过乳头,然后对接行ERP来胰管引流。EUS-TMD是指引流管或支架通过胃壁或肠壁直接进入主胰管的跨壁引流,包括经胃壁的EUS胰胃吻合术(EUS-pancreaticogastrostomy, EUS-PGS)和经十二指肠的EUS胰十二指肠吻合术(EUS-pancreaticoduodenostomy, EUS-PDS)。

EUS-PD治疗有效性与安全性良好。近期一项荟萃分析显示,EUS-PD的技术成功率为81.4%,临床成功率为84.6%,不良事件的总体发生率为21.3%^[24]。不良事件包括疼痛(15.9%)、急性胰腺炎(5%)、穿孔(3.1%)、胰漏(2.3%)等^[24-25]。对于两种不同的引流方式,Nakai等^[26]比较12项研究中的EUS-RV与11项研究中的EUS-TMD,技术成功率分别为55.6%和93.8%,EUS-RV成功率明显较低,主要因为导丝操作困难,不易通过乳头/吻合口。但Dalal等^[27]得出相反的结论,认为EUS-RV比EUS-TMD成功率更高(52.3%比40.9%),且不良事件相对较少。从整体的研究及临床经验来看,对于正常解剖结构的病人,EUS-RV或许是首选的PD方案,因为其更符合解剖生理,且不良事件更少。EUS-TMD是否只能作为EUS-RV不成功后的替补方案,尚需多中心、大样本的研究来验证。

EUS-PD目前仍是一项极具挑战性的内镜技术,需要操作医师同时具有丰富的EUS和ERCP操作经验。Tyberg等^[28]认为,即使是经验丰富的介入内镜医师,要掌握EUS-PD也至少需完成40例手术。EUS-PD技术难度并不亚于ERCP,相较于ERCP学习曲线^[29],还需要更多的操作数量才可能熟练掌握EUS-PD,手术的成功率、操作时间、不良事件等仍有更大的改善空间。

2.2 PPC引流术

PPC是急性胰腺炎或慢性胰腺炎后期并发症。EUS引导下PPC引流术目前已成为一种成熟的治疗方法。PPC广义上包括单纯的假性囊肿和胰腺

包裹性坏死(walled-off necrosis, WON)。EUS在诊断PPC方面比CT或超声更有优势,灵敏度93%~100%,特异度92%~98%^[30],且可以分析囊肿内坏死物成分含量来区分PPC与WON^[31]。另外,EUS-细针穿刺活检评估囊肿液有助于区分PPC与其他恶性囊性疾病^[32]。

对EUS介入治疗的指征和时机存在争议。我国专家共识推荐如下:①囊肿持续4周以上;②直径>6 cm;③继发压迫症状;④囊肿进行性增大;⑤合并囊内感染伴胰源性门静脉高压等并发症。具备①,同时存在②③④⑤中的任意一项时,建议采取介入治疗^[33]。延迟(>4周)内镜干预,临床成功率较高,再干预率和死亡率较低^[34]。然而当病人存在强烈的干预指征如严重感染、器官衰竭等时,早期(<4周)干预具有相似的技术和临床成功率以及不良事件发生率,且可能改善器官衰竭、降低死亡率^[35]。

与PPC经皮引流相比,经内镜或腹腔镜PPC引流术的短期手术并发症发生较少,住院效果较好^[36];对于坏死物含量<30%的PPC引流具有相似的疗效^[37]。由于内镜下引流创伤比腹腔镜更小,所以更易被病人接受。对于单纯的PPC,应用塑料支架与金属支架的临床成功率和远期效果相似;对于坏死物含量≥30%的WON,应考虑使用口径大的金属支架^[31, 38]。最早时,完全或部分覆膜的SEMS因直径较大被应用于改善引流^[39-40],但支架移位事件的发生率较高。LAMS是目前被推荐为WON引流的首选支架^[41]。其在技术上易于放置^[42],不良事件较少,更重要的是后续可实施内镜下坏死组织清除术^[43]。然而,如在原位长时间放置,不良事件发生率也会增加,如出血和穿孔^[44]。因此,建议在放置1个月内移除LAMS^[38, 42]。移除LAMS后放置塑料支架与否并不能减少胰周液体体积聚的复发,尤其对于WON伴有胰管离断综合征的病人^[45]。另外,LAMS使用成本高也是不容忽视的问题^[46],降低使用成本将有助于其广泛应用。

2.3 胰腺肿瘤介入治疗术

2.3.1 EUS引导下消融术

对于无法手术的胰腺癌或胰腺囊实性肿瘤病人,可选择消融术进行姑息性治疗^[47]。EUS引导下消融术分为药物消融和物理消融。药物消融主要采用化疗药物、无水乙醇等消融剂。物理消融主要是射频消融和光动力治疗。EUS引导下药物消融在PPC的治疗中应用更多。乙醇是最早应用于囊

性肿瘤的消融剂,治疗后囊性肿瘤完全消退率在不同的研究中存在差异,在 35%~79% 之间^[48]。同时也存在较多的并发症,如腹痛、急性胰腺炎等。近期研究显示不含乙醇的化疗药物如紫杉醇或紫杉醇联合吉西他滨消融可获得相似的消退效果,且能长期缓解,并发症发生却比乙醇明显减少^[49-50]。EUS 引导下的射频消融和光动力治疗,成为胰腺实性肿瘤的补充治疗方式,如胰腺导管腺癌和胰腺神经内分泌肿瘤^[51]。EUS 引导下的射频消融对恶性实性肿瘤的完全消退率为 55%~100%,优于药物消融,且无额外的手术相关不良事件发生^[48]。尽管 EUS 引导下射频消融已被认为治疗胰腺癌安全可行,但其有效性及整体的生存期是否获益仍有待评估^[52]。EUS 引导下消融术将来可能会成为一种广泛应用于治疗胰腺肿瘤的替代方法,需大量高质量的研究为临床提供标准化的治疗方案。

2.3.2 EUS 引导下腹腔神经丛松解术

EUS 引导下腹腔神经丛松解术(endoscopic ultrasound-guided celiac plexus neurolysis, EUS-CPN)主要用于治疗胰腺癌或慢性胰腺炎引起的顽固性疼痛。向腹腔神经丛区域注射乙醇或局部麻醉药毁损神经以缓解疼痛。根据穿刺部位,主要可分为 3 种不同的技术方式:①中心注射(central injection, CI),在腹腔动脉根部前方注射;②双侧注射(bilateral injection, BI),在腹腔动脉根部两侧注射;③腹腔神经节神经松解术(celiac ganglia neurolysis, CGN),在腹腔神经节中部注射^[53]。EUS-CPN 的有效性从 50% 到 94% 不等,缓解持续时间为 4~8 周^[54]。远处转移以及潜在的神经节和腹腔神经丛受侵犯等是影响有效性的因素^[55]。EUS-CPN 与肿瘤乙醇消融术相结合可更好地缓解疼痛^[56]。EUS-CPN 的围术期可出现短暂的疼痛加剧、腹泻或低血压,罕见且严重的不良事件包括腹膜后出血、缺血性并发症和脓肿形成^[57]。EUS-CPN 并发症发生较多、远期疗效差,目前应用应更谨慎。更长的疼痛缓解期和更少的不良事件发生仍被期待。

3 结语

EUS 介入技术为胆胰疾病提供了更多可行的治疗方案。相较于外科手术和经皮途径治疗,EUS 介入在获得相似临床效果的同时,住院时间更短,生活质量更高。EUS 引导下 PPC 引流以及胆胰管的引流技术已逐渐标准化并被写入相应指南。覆

膜 SEMS 和 LAMS 的应用为 EUS 介入技术扩大了适应证,提高了有效性和安全性。当然,目前仍需要更多的专用器械开发以发挥 EUS 介入技术的优势。将来,EUS 介入治疗的地位也会发生改变,不仅是有效的替代治疗方案,还可作为某些疾病如消化道重建术后胆管结石和梗阻性黄疸内镜治疗的首选。但胆胰疾病的 EUS 介入技术操作相对困难,且存在一定风险,如 EUS-BD、EUS-PD、EUS-CPN 等。目前,国内只有较大的内镜中心可开展相关操作,但越来越多的国内学者重视这些高难度技术并积极推广,建立专业化的培训基地也将有助于该领域的发展,未来可期。

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· 简讯 ·

《诊断学理论与实践》征稿、征订启事

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