

EUS引导下介入治疗现状

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Progress in research of endoscopic ultrasound-guided interventional therapy

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Abstract

Endoscopic ultrasound (EUS)-guided

interventional therapy is an important research direction of EUS, and it mainly includes EUS-guided celiac plexus neurolysis (EUS-CPN), EUS-guided pseudocyst drainage, EUS-guided biliary drainage (EUS-BD), and EUS-guided fine needle injection (EUS-FNI). The therapeutic effect of EUS-CPN was superior to that of traditional analgesic therapy. No matter whether the first CPN therapy is effective, the effect of a second CPN is limited. Choosing unilateral or bilateral injection is related to operators' habits and proficiency, and there is no obvious difference in therapeutic effect. EUS-guided pseudocyst drainage is the best choice for patients who have the indications for drainage. The efficacy and safety of EUS-BD have been confirmed. EUS-guided ethanol injection is currently the best therapeutic method for patients with pancreatic neuroendocrine tumors who are not suitable for or unwilling to undergo surgery. The therapeutic value of EUS-RFA and EUS-FNI for pancreatic cancer remains to be further confirmed.

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Key Words: EUS-guided interventional therapy; EUS-guided celiac plexus neurolysis; EUS-guided pseudocyst drainage; EUS-guided biliary drainage; EUS-guided fine needle injection

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背景资料

近几年, 超声内镜的应用范围逐渐扩展至介入治疗领域, 主要包括EUS引导下腹腔神经丛阻滞术(EUS-guided celiac plexus neurolysis, EUS-CPN)、超声内镜引导下胰腺假性囊肿引流、EUS引导下胆管引流(EUS guided biliary drainage, EUS-BD)、胰腺肿瘤超声内镜引导下肿瘤注射治疗(EUS guided fine needle injection, EUS-FNI)等, 各种治疗方法效果及实用价值存在争议。

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■ 研究前沿

EUS引导下介入治疗是EUS领域热门方向, 各种新的治疗方式不断出现, 其治疗方式的选择以及疗效存在诸多争议, 本文将系统地阐述EUS引导下介入治疗的现状, 探讨相关热点问题。

摘要

内镜超声检查术(endoscopic ultrasonography, EUS)引导下介入治疗是目前EUS发展的重要方向, 主要包括EUS引导下腹腔神经丛阻滞术(EUS-guided celiac plexus neurolysis, EUS-CPN)、EUS引导下胰腺假性囊肿引流、EUS引导下胆管引流(EUS guided biliary drainage, EUS-BD)、超声内镜引导下肿瘤注射治疗等。EUS-CPN效果优于传统镇痛治疗; 无论是首次CPN治疗是否有效, 再次进行CPN治疗价值有限; 选择单侧注射还是双侧注射与操作者习惯及熟练程度有关, 在治疗效果上目前没有明显差异。EUS引导下假性囊肿引流为符合引流条件的患者首选方法。EUS-BD的有效性和安全性基本已经得到了认可。EUS引导下酒精注射治疗目前是不适合手术或不愿意接受手术的胰腺神经内分泌肿瘤患者最佳的选择; 内镜超声引导下射频消融与EUS引导下胰腺癌注射治疗价值有待进一步证实。

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关键词: 超声内镜引导下介入治疗; EUS引导下腹腔神经丛阻滞术; EUS引导下胰腺假性囊肿引流; EUS引导下胆管引流; EUS引导下肿瘤注射治疗

核心提要: 内镜超声检查术(endoscopic ultrasonography, EUS)引导下腹腔神经丛阻滞术、EUS引导下胰腺假性囊肿引流、EUS引导下胆管引流的治疗有效性和安全性基本已经得到了认可, 值得临床推广。超声内镜引导下肿瘤注射治疗(EUS guided fine needle injection, EUS-FNI)是值得进一步研究的方向, 目前EUS引导下酒精注射治疗是不适合手术或不愿意接受手术的胰腺神经内分泌肿瘤患者最佳的选择; 胰腺癌内镜超声引导下射频消融与EUS-FNI治疗价值有待进一步证实。

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0 引言

随着超声内镜引导下细针穿刺活检[内镜超声检查术(endoscopic ultrasonography, EUS) guided fine needle aspiration, EUS-FNA]技术的发展与

广泛普及, 超声内镜的诊断价值已经得到临床医生的广泛认可, 近几年, 超声内镜的应用范围逐渐扩展至介入治疗领域, 主要包括腹腔神经丛阻滞术(celiac plexus neurolysis, CPN)、假性囊肿、胆管引流(biliary drainage, BD)、肿瘤注射治疗等^[1,2], 下文我们将进一步探讨超声内镜引导下介入治疗的应用现状。

1 EUS引导下腹腔神经丛阻滞术

CPN是指将无水乙醇或者苯酚注射到神经丛或神经节里面或者周边, 从而永久性破坏神经丛或神经节。CPN治疗一般用来缓解疼痛及减少麻醉类药品的使用剂量。CPN操作可经皮穿刺注射、术中注射以及EUS引导下注射, EUS引导下腹腔神经丛阻滞术(EUS-guided celiac plexus neurolysis, EUS-CPN)的优势在于穿刺距离短, 通过多普勒显像可精确的避开血管。Wiersema等^[3]在1996年首次报道了EUS-CPN, 研究中纳入30例腹膜后恶性疾病导致腹痛的患者, 结果显示EUS-CPN治疗后患者疼痛评分显著降低。此后, 多个随机对照研究^[4-6]及荟萃分析结果证明, 与传统镇痛治疗相比, EUS-CPN效果更好。

一般EUS-CPN缓解疼痛有效期限一般为12 wk^[7], 当疼痛再次加剧, 部分患者会选择再行CPN治疗。1项纳入96例患者的随机对照研究^[8]结果显示, 实验组接受EUS-CPN的患者在3 mo后吗啡平均使用剂量低于未接受EUS-CPN对照组患者, 但实验组有15%的患者吗啡使用剂量没有减少, 这部分患者再次进行EUS-CPN治疗后吗啡剂量依旧没有减少。1项纳入24例患者的临床研究^[7]结果显示, 首次行CPN治疗疼痛缓解率为69%, 再次行CPN治疗疼痛缓解率仅为24%。无论是首次CPN治疗是否有效, 再次进行CPN治疗价值有限。

在进行EUS-CPN治疗时, 我们一般选择腹腔干与腹主动脉夹角处进针注射, 目前有单侧注射和双侧注射两种方法。1项随机对照研究^[9]结果显示, 2种方法在疼痛缓解持续时间、完全缓解患者比例及麻醉药物使用剂量减低这几个疗效评估指标的差异均没有统计学意义。选择单侧注射还是双侧注射与操作者习惯及熟练程度有关, 在治疗效果上目前并没有发现明显差异。

传统EUS-CPN是进行腹腔神经丛注射, 有

学者^[10]认为, 直接进行腹腔神经节注射效果会更好。80%的患者腹腔神经节可通过超声显像, 表现为位于腹主动脉与左侧肾上腺之间腹腔干左肾动脉水平, 椭圆形低回声结节状结构。最近一项随机对照研究^[11]结果显示, 腹腔神经节注射效果优于腹腔神经丛注射。目前关于腹腔神经丛注射与腹腔神经节注射效果的优劣比较研究较少, 需要更大规模的临床研究验证以上结论。

2 EUS引导下胰腺假性囊肿引流

对于假性囊肿, 如果直径>6 cm, 持续6 wk以上并且出现症状, 囊壁与消化道管壁距离<1 cm, 可以进行EUS引导下引流。对于符合条件的假性囊肿引流, EUS引导下引流成功率超过90%^[12,13]。与手术引流、经皮穿刺引流相比, EUS引导下引流具有显著优势。一篇综述^[14]数据显示, 手术引流并发症发生率28%-34%、死亡率1.0%-8.5%, 经皮穿刺引流并发症发生率18%、死亡率2%, EUS引导下穿刺引流并发症发生率1.5%、死亡率0%。EUS引导下胰腺假性囊肿引流传统一般使用双猪尾塑料支架, 近年来出现了全覆膜金属支架, 对于两种支架的选择, 存在诸多争议。一项回顾性研究^[15]结果显示, 塑料支架和金属支架在技术成功率、引流成功率、并发症发生率方面均无显著差异, 但是金属支架操作时间更短。虽然金属支架更易于操作, 直径更粗, 引流更充分, 但是其价格昂贵并且容易移位。最新出现的蘑菇头全覆膜金属支架, 两端有凸缘用于固定, 形似哑铃。已有多个研究^[16-18]结果显示, 这种新式的金属支架对于胰腺假性囊肿的引流安全并且有效。最近的一项回顾性临床研究^[19]结果显示, 蘑菇头全覆膜金属支架技术成功率及引流成功率均高于传统金属支架。目前EUS引导下假性囊肿引流已经成为符合条件的患者首选方法^[20]。

3 EUS引导下胆管引流

内镜逆行胰胆管造影(endoscopic retrograde cholangiopancreatography, ERCP)为胆管梗阻引流的首选方法^[21], 对于插管困难、ERCP操作失败的患者, 可以进行乳头切开、经皮穿刺引流(percutaneous transhepatic biliary drainage, PTBD)及手术引流, 近期出现了一种新的可选择方案-EUS引导下胆管引流(EUS

guided biliary drainage, EUS-BD)。在2001年, Giovannini等^[22]首次提出EUS-BD的概念, EUS-BD可以让患者免于经皮穿刺引流的不便, 并且可以在ERCP失败后立刻进行操作, 减少了患者获得有效治疗的等待时间。EUS-BD主要包括2种路径, 即肝外胆管引流和肝内胆管引流。肝外胆管引流时, 一般直接经消化道官腔穿刺胆总管后放置支架实现胆管引流, 或者穿刺胆总管后将导丝经乳头引出实现对接, 这样可以避免经胃肠壁放置支架。经消化道穿刺肝外胆管引流时, 可以经胃穿刺, 也可经十二指肠穿刺, 对于穿刺路径的选择, 一项荟萃分析^[23]结果显示, 两种穿刺方法其有效性、成功率及并发症发生率都没有显著差异。因此, 穿刺路径的选择, 主要还是依赖于操作医生个人经验。肝内胆管引流一般是经胃穿刺肝左叶, 偶尔也会经食管或空肠穿刺。目前的临床研究^[24-27]结果显示, EUS-BD的成功率波动在93%-100%, 术后并发症发生率波动在9%-19%。最近的一项荟萃分析^[28]结果显示, EUS-BD成功率为90%, 并发症发生率为17%。EUS-BD的有效性和安全性基本已经得到了广大临床医师的认可。但是, 需要注意的是, EUS-BD的高成功率主要是针对胆总管远端梗阻, 即肝外胆管引流, 肝内胆管穿刺引流并发症非常高且成功率很低^[29]。

根据目前的研究结果显示, EUS-BD并发症发生率高于ERCP, 因此, ERCP依旧为胆管梗阻引流首选方法, 只有在ERCP失败时, 才考虑选择EUS-BD。对于ERCP失败后是选择PTBD还是EUS-BD, 目前没有统一意见。Khashab等^[30]研究结果显示接受了PTBD治疗的患者约45.1%的患者需再次进行介入治疗, 高于EUS-BD(15.3%)。Bapaye等^[31]的研究结果显示EUS-BD(92%)引流成功率高于PTBD(46%)。一项随机对照研究结果显示, 并发症发生率PTBD高于EUS-BD(25% vs 15.3%)。目前, 大部分研究认为, EUS-BD并发症发生率低于PTBD, 其有效性及操作成功率相当, 需要大规模多中心前瞻性研究明确2种方法的优劣。

4 EUS引导下肿瘤治疗

随着超声内镜引导下细针穿刺技术的广泛普及, 以穿刺技术为基础的肿瘤介入治疗迅速发

创新盘点
本文阐述了EUS引导下主要的介入治疗方法现状, 并针对各种治疗手段存在争议的问题进行了较为系统地探讨。

应用要点

EUS-CPN效果优于传统镇痛治疗, 无论首次CPN治疗是否有效, 再次进行CPN治疗价值有限, 选择单侧注射还是双侧注射与操作者习惯及熟练程度有关, 在治疗效果上没有明显差异. EUS引导下假性囊肿引流为符合引流条件的患者首选方法. EUS-BD的有效性和安全性基本已经得到了认可. EUS引导下酒精注射治疗目前是不适合手术或不愿意接受手术的胰腺神经内分泌肿瘤患者最佳的选择, 胰腺癌内镜超声引导下射频消融与EUS-FNI治疗价值有待进一步证实.

展, 目前主要包括射频消融、酒精注射、肿瘤注射治疗技术.

4.1 EUS引导下射频消融 最近的一项荟萃分析结果显示, 内镜超声引导下射频消融(EUS radio frequency ablation, EUS-RFA)治疗晚期胰腺癌技术成功率100%^[32], 这种方法可操作性强并且安全性良好^[33,34], 但目前没有疗效相关研究. 有专家^[33]认为, 胰腺癌射频消融治疗除直接杀伤肿瘤细胞外, 还可激发机体免疫系统增强抗肿瘤反应, 同时增强肿瘤血供. Pai等^[35]尝试将EUS-RFA应用于胰腺囊性肿瘤及胰腺神经内分泌肿瘤, 结果显示其安全性良好, 并且治疗效果良好, 治疗后病灶完全消失或直径减少一半以上. Lakhtakia等^[36]利用EUS-RFA技术治疗胰岛素瘤, 接受治疗的3例患者在3 mo后症状完全消失. 虽然EUS-RFA治疗相关研究较少, 但根据已有的研究结果, 这是一种值得期待的治疗手段.

4.2 EUS引导下酒精注射 EUS引导下酒精注射治疗胰腺神经内分泌肿瘤是一种新的微创治疗手段, Jürgensen等^[37]最先对EUS引导下酒精注射治疗胰岛素瘤进行了报道, 随后Levy等^[38]也进行了相关研究, 结果显示治疗后患者低血糖症状迅速改善. 我国教授Qin等^[39]也发表了EUS引导下究竟注射治疗胰岛素瘤的病例报道, 进一步验证了这种治疗方法的安全性以及有效性. 最近的一篇综述^[40]结果显示, 其技术成功率达100%, 对于有症状的胰岛素瘤, 临床症状缓解率达100%, 对于无症状的患者, 肿瘤完全消除率达70%. 术后并发症主要为轻度胰腺炎, 发生率大约16.5%^[41], 严重并发症主要包括出血和十二指肠溃疡及胰管溃疡, 发生率约4.6%^[42,43]. EUS引导下胰腺神经内分泌肿瘤治疗是一种稳定安全有效的微创治疗方法, 虽然其长期治疗效果有待观察, 但是目前这是不适合手术或不愿意接受手术的胰腺神经内分泌肿瘤患者最佳的选择.

4.3 EUS引导下肿瘤注射 胰腺癌富含结缔组织, 形成化疗抵抗的细胞屏障, 这可能是导致其传统化疗效果不佳的原因之一. 近几十年来, 临床医生尝试各种治疗方法, 但是胰腺癌的生存率依旧没有明显改善. 因此, 有专家提出, 在超声内镜引导下肿瘤注射治疗(EUS guided fine needle injection, EUS-FNI), 即在超声内镜引导下穿刺, 直接将抗肿瘤药物注入瘤体内

部, 希望能改善晚期胰腺癌治疗效果. 2000年, Chang等^[44]将T淋巴细胞在EUS引导下注入8例晚期胰腺癌患者瘤体, 结果显示2例部分应答, 1例轻微应答, 平均生存期13.2 mo, 后来一些小规模报道了较为严重的并发症, 且其治疗效果不确切, 抗肿瘤细胞注射治疗相关研究基本停止. 2003年, Hecht等^[45]尝试注射腺病毒ONYX-015, 研究纳入21例无法手术的胰腺癌患者, 同时接受系统性化疗, 治疗持续8 wk, 1次/wk, 2例患者病灶缩小, 2例无明显变化, 11例肿瘤进展, 其他患者因治疗过程中出现毒性反应中止治疗. 2007年, Irisawa等^[46]在EUS引导下将树突状细胞注入7例吉西他滨化疗失败的晚期胰腺癌患者瘤体内, 治疗过程中无明显不良反应, 但是其平均生存期仅9.9 mo. 2012年, Hecht等^[47]将包含人类肿瘤坏死因子基因的腺病毒注入胰腺癌患者瘤体内, 治疗持续5 wk, 同时进行系统性化疗, 毒性反应与注射剂量相关, 4例患者出现轻微不良反应, 包括2例胰腺炎, 1例低血压, 1例黄疸. 5例患者接受了最大剂量注射, 最终4例接受了手术治疗并且手术切缘阴性, 3例生存期超过24 mo. 其后, Levy等^[48]研究吉西他滨瘤内注射治疗的效果, 结果显示瘤内注射吉西他滨安全性良好, 但疗效有待进一步证实. 胰腺癌EUS-FNI作为一种姑息性辅助治疗方法, 相关研究还处于起步阶段, 存在很多问题和困难, 要想让更多患者从中受益, 任重而道远.

EUS引导下穿刺不仅可以向肿瘤内部注射药物, 还可以置入放射性粒子, 进行短距离放疗, 应用最为广泛的粒子包括碘125、钋103、铈192. Sun等^[49]将碘125粒子在超声引导下置入15例晚期胰腺癌患者瘤体内, 结果显示患者中位生存期为10.6 mo, 27%的患者对放疗部分反应. 另一项纳入22例晚期胰腺癌患者的研究^[50], 结合全身化疗, 结果显示患者生存期无明显改善. 这种治疗方式最大的问题是放射线泄露, 但是这些放射线在人体组织中穿透性差, 辐射范围很小, 放射性泄漏风险较小.

5 结论

EUS最初作为一种无创的影像学检查方法用于消化道疾病的辅助诊断, 随后出现EUS-FNA, 其发展成为消化道及其邻近器官疾病的定性诊断方法, 经过数年的探索与经验积累,

EUS-FNA的诊断水平趋于稳定, 为临床医生广泛接受。其后, 在EUS-FNA的基础上, 出现了EUS引导下的各种治疗手段, 目前EUS引导下的各种引流技术已经广泛开展。EUS引导下肿瘤治疗是EUS引导下介入治疗继续发展的重要方向, 目前, 需要更多的研究明确其疗效及应用指征。

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□ 同行评价
本文选题围绕超声内镜介入治疗最新研究进展, 选题紧跟临床前沿, 适合大部分消化科及介入科医师阅读, 有一定的发表价值。

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