

内镜黏膜下剥离术治疗早期食管癌及癌前病变的进展

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Endoscopic submucosal dissection for treatment of early esophageal cancer and precancerous lesions

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Abstract

Esophageal cancer is the eighth most common form of cancer worldwide. Advances in endoscopic therapy have resulted in dramatic changes in the way early esophageal cancer and precancerous lesions are managed. Endoscopic submucosal dissection (ESD) is a newly developed resection technique that is able to achieve a high R0 resection rate and a low local recurrence rate. Techniques of ESD have become established as standard methods of endoscopic resection. This review addresses some of the recent developments in the field of ESD for early esophageal cancer and precancerous lesions.

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Key Words: Endoscopic submucosal dissection; Esophageal cancer; Robot; Thulium laser; Treatment

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摘要

食管癌的发病率在世界范围内居恶性肿瘤第8位, 内镜下治疗技术的发展给早期食管癌及癌前病变的治疗带来了巨大的变革。内镜黏膜下剥离术(endoscopic submucosal

背景资料

内镜黏膜下剥离术(endoscopic submucosal dissection, ESD)是在进行黏膜下注射后使用特殊电刀逐渐分离黏膜层与固有肌层之间的组织, 将病变黏膜及黏膜下层完整剥离的方法。自Oyama等从2000年开始将ESD引入早期食管癌的治疗以来, 经过多年的发展, ESD作为治疗早期食管癌及癌前病变的一种标准方法已经被广泛接受。

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■ 研发前沿

软式内镜机器人系统、铥激光、新型电刀等应用于ESD治疗有望降低内镜下治疗的难度、提高治疗的安全性, 但评价治疗效果仍需要更多临床中心的经验以及长期的随访观察。

dissection, ESD)是一种新型内镜下切除技术, 可以获得更高的完全切除率和更低的复发率, 目前已成为内镜下切除治疗的标准方法。本文就ESD治疗早期食管癌及癌前病变的进展情况作一综述。

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关键词: 内镜黏膜下剥离术; 食管癌; 机器人; 铥激光; 临床应用

核心提示: 随着消化内镜技术的不断发展和内镜医师经验的提升, 越来越多的早期食管癌及癌前病变被发现。内镜黏膜下剥离术(endoscopic submucosal dissection)作为一种安全、有效、微创的治疗手段, 近年来得到了快速发展, 在世界范围内也越来越流行, 成为目前治疗符合适应证的早期食管癌和癌前病变的标准方法。

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0 引言

早期食管癌是指病灶局限于黏膜层和黏膜下层, 不伴有淋巴结转移的食管癌; 食管的癌前病变是指业已证实与食管癌发生密切相关的病理变化, 主要包括鳞状上皮不典型增生等。近年来随着消化内镜技术的不断发展和内镜医师经验的提升, 越来越多的早期食管癌及癌前病变被发现^[1-3]。

与传统的外科手术相比, 内镜下切除治疗早期食管癌及癌前病变可保留食管的正常器官结构及避免外科手术较高的并发症和死亡率^[4-6], 且可以取得与外科手术相当的疗效^[7-9]。内镜下黏膜切除术(endoscopic mucosal resection, EMR)是较早应用于临床的内镜下切除技术, 主要包括标记、注射、圈套、处理创面等步骤, 这一技术方法简便, 创伤小, 并发症少^[10,11], 但是对于直径较大的病变, 往往需行多次分片切除, 分片切除给切除标本的病理评估带来了困难, 而且增加了复发的风险^[12-15], 故主要用于直径20 mm以下病变的治疗。内镜黏膜下剥离术(endoscopic submucosal dissection, ESD)是在EMR基础上发展而来的一项新型内镜下切除技术, 他是在进行黏膜下注射后使用特

殊电刀逐渐分离黏膜层与固有肌层之间的组织, 将病变黏膜及黏膜下层完整剥离的方法^[16]。ESD在切除病变位置、大小方面所受限制较小, 可提供准确的病理诊断分期, 在完整切除率和复发率方面均优于传统的EMR^[17-19]。自Oyama等^[20]从2000年开始将ESD引入早期食管癌的治疗以来, 经过多年的发展, ESD作为治疗早期食管癌及癌前病变的一种标准方法已经被广为接受^[21-25]。

1 食管ESD治疗经过

1.1 适应证 理论上只要未侵及固有肌层、无淋巴及血管转移, 不论病灶位置及大小, 均可用ESD切除。我国于2012年制定的消化系黏膜病变内镜黏膜下剥离术的专家共识意见中, ESD治疗早期食管癌及癌前病变适应证包括以下几项: (1)大于15 mm的食管高级别上皮内瘤变; (2)早期食管癌: 结合染色、放大和超声内镜等检查, 确定病变的范围和浸润深度, 局限于M1(病变局限于上皮内, 未突破基底膜)、M2(病变突破基底膜, 浸润黏膜固有层)、M3(病变浸润黏膜肌层)或SM1(病变浸润黏膜下层上1/3)且临床没有血管和淋巴管侵犯证据的高、中分化鳞癌; (3)伴有不典型增生和癌变的Barrett食管; (4)姑息性治疗, 适于侵犯深度超过SM1、低分化食管癌、心肺功能较差不能耐受手术的高龄患者及拒绝手术者, 并需结合放疗^[26]。对于病变范围大于3/4环周、切除后狭窄风险大的病变是否行内镜下切除, 国内也已达成共识, 认为是一相对适应证, 但应向患者充分告知术后狭窄等风险。

1.2 禁忌证 明确发生淋巴结转移的病变; 若术前判断病变浸润至黏膜下深层, 有相当比例患者内镜下切除无法根治, 原则上应行外科手术; 一般情况差、无法耐受内镜手术者。相对禁忌证: 非抬举征阳性; 伴发凝血功能障碍及服用抗凝剂的患者, 在凝血功能纠正前不宜手术; 术前判断病变浸润至黏膜下深层, 患者拒绝或不适合外科手术者^[27]。

1.3 主要操作步骤 (1)标记: 通过卢戈液染色^[28-30]或窄带成像放大内镜^[31,32]明确病变范围, 用氩离子凝固术(argon plasma coagulation, APC)等于病变边缘5 mm处电凝标记切除范围; (2)黏膜下注射: 于病变边缘标记点外侧进行多点黏膜下注射, 将病灶抬起, 使黏膜层与肌层充分分离, 对防止穿孔非常重要^[33], 必要时可反复

■ 相关报道

随着ESD技术的广泛应用, 有关ESD的治疗设备也不断被开发应用, 刘枫等对ESD使用的内镜、黏膜下注射液、先端附件、切开刀等作了相关介绍, 可使国内同道更方便快捷地了解ESD最新器械的相关进展。

注射. 目前国内常用的注射液体为生理盐水加入肾上腺素和靛胭脂的混合液, 肾上腺素体积分数约为0.0005%, 能使局部血管收缩以止血和减少出血. 靛胭脂可使术者更容易地分辨剥离范围, 监测剥离深度, 减少穿孔可能, 这种混合液优点是配置简单、成本较低, 缺点是黏膜下水垫隆起持续时间较短, 其他应用的注射液体还有甘油果糖、透明质酸钠^[34]、纤维蛋白原、高渗盐水、高渗葡萄糖等; (3)环形切开: 用Hook刀^[35]等沿标记点外侧环周切开黏膜, 一般首先从病变远侧端开始, 黏膜切开时要深至黏膜下层, 否则操作过程中较易造成出血; (4)黏膜下剥离: 当病变四周充分切开后, 用IT刀^[36]等对黏膜下层进行剥离, 直至病变完整剥离; (5)创面处理: 在ESD操作过程中和术后对创面上裸露血管或出血点用止血钳、APC等电凝处理以预防和控制出血, 一般情况下尽量不要过早应用钛夹以免影响进一步的剥离. 完成剥离后常规应用钛夹缝合大部分创面, 可局部喷洒胃黏膜保护剂保护创面; (6)标本处理: 将切除病灶标本展平, 染色并用细针固定四周, 测量标本大小, 4%甲醛溶液固定后送病理检查, 切除标本的病理学报告需描述病变的大体形态、部位、大小、组织学类型、浸润深度及切缘、是否有淋巴管和血管受累等. 精确的病理组织学诊断是评价ESD治疗效果和决定是否需要追加治疗所不可缺少的.

1.4 术后处理 术后第1天患者应禁食, 常规予补液、抑酸、止血等对症支持治疗. 观察有无头颈胸部皮下气肿、消化道出血, 进行必要的实验室和影像学检查. 如临床表现和相关检查无异常, 术后第2天可进流质, 第3天可进软食, 此后再逐步恢复正常饮食. 出院后继续口服质子泵抑制剂^[37,38]和胃黏膜保护剂^[39]直至溃疡愈合, 一般术后4 wk左右人工溃疡即可愈合. 术后2、6、12 mo复查胃镜, 此后至少每年复查1次, 了解溃疡愈合情况, 病变有无残留和复发.

2 食管ESD有效性和安全性

目前认为ESD治疗食管病变疗效理想, 并发症相对少见且可控, 近期发表的多篇东西方ESD研究也证实了上述观点. Toyonaga等^[40]回顾了日本1261例经ESD治疗的消化系早癌及癌前病变患者(其中食管111例)的临床资料, 食管ESD的完全切除率和治愈性切除率分别达到

95.7%和81.2%, 没有术后出血和穿孔病例, 在53.4 mo(0.07-98.6 mo)的中位随访时间里, 未见复发和与疾病相关的死亡, 5年生存率为81.6%, 研究结果表明ESD疗效显著, 但在根治性方面弱于传统的外科手术治疗. Probst等^[22]分析了2007-08/2014-03 111例经ESD治疗的早期食管癌患者(其中腺癌87例, 鳞癌24例)的临床资料, 这是一项来自德国的前瞻性研究, 发现早期食管腺癌和鳞癌的完整切除率分别为95.4%和100%, 完全切除率分别为83.9%和91.7%, 治愈性切除率分别为72.4%和45.8%, 治疗过程中没有患者出现穿孔, 有13例(11.7%)患者出现术后狭窄, 但经过胃镜下球囊扩张治疗后均缓解, 1例(0.9%)患者出现出血, 成功予内镜下金属夹封闭处理, 经过平均24.3 mo(腺癌)和38.0 mo(鳞癌)的随访, 腺癌组2例(2.4%)出现复发, 鳞癌组未见复发, 疾病特异性生存率分别为97.7%和95.8%, 总生存率分别为96.6%和66.7%, 得出结论ESD治疗早期食管腺癌和鳞癌是安全有效的, 对于ESD手术时间长和费用高的不足, 研究者指出低复发率可以避免再次治疗所需的时间及金钱花费, 也可以使术后随访的频次相应减少, 这使得上述不足是可以接受的. Higuchi等^[41]报道了一项关于ESD治疗浅表型食管肿瘤的II期临床研究, 共纳入56例病变, 其中鳞癌49例, 高级别上皮内瘤变5例, 腺癌2例, 结果同样表明ESD治疗浅表型食管肿瘤是有效且相对安全的.

3 ESD治疗新进展

3.1 机器人平台下的ESD 软式内镜机器人系统^[42] 是近年来内镜治疗领域的一个革命性产物, 大多数此类机器人具有两个机械手臂, 通过电缆控制机械手臂, 可完成抓取、牵拉、切开、切除、止血等操作^[43], 可有效降低内镜下治疗的难度. 目前已有多篇文献肯定了其应用于ESD治疗的可行性和安全性^[44-46], 但评价内镜机器人的治疗效果仍需要更多临床中心的经验以及长期的随访观察.

3.2 钺激光应用于ESD 钺激光主要依靠组织中的水分子吸收激光而发挥作用, 实际波长可以根据临床需要进行调节. 钺激光应用于内镜治疗具有以下优点: (1)止血效果好, 视野清楚, 安全性更好; (2)热损伤小, 对组织的伤害少; (3)切割创面整齐, 复发率降低; (4)在正常操作

■创新盘点

本文对ESD治疗早期食管癌及癌前病变的临床应用情况和技术方法做了阐述, 并对ESD治疗领域的新进展如机器人平台下的ESD、钺激光应用于ESD治疗等做了简明扼要的介绍.

应用要点

文中对ESD治疗早期食管癌及癌前病变的禁忌证、适应证、主要操作步骤、术后处理等做了相关介绍, 对于临床工作具有一定的指导和借鉴意义。

下不会对组织造成意外的损伤, 水下操作非接触组织时, 激光能量在水中瞬间被水吸收; (5) 不需要负极板, 对体内有金属植入物的患者没有影响, 比如血管支架、心脏起搏器、骨科耗材等。2013年来自韩国的Cho等^[47]发表了关于铥激光应用于ESD的研究, 取得了较好的临床效果, 未见明显并发症发生, 但关于铥激光技术应用于ESD的有效性及安全性仍需进一步探讨。

4 结论

ESD作为一种安全、有效、微创的治疗手段, 近年来得到快速发展, 在世界范围内也越来越流行, 成为目前治疗符合适应证的早期食管癌和癌前病变的标准方法。考虑到ESD技术要求高, 学习曲线较长^[48-50], 而食管ESD对技术的要求更加严格^[51], 需要对操作医生进行更多的技术培训和指导。未来我们期待更多大样本多中心随机对照研究的开展和ESD技术设备的革新, 使ESD治疗早期食管癌及癌前病变日益规范化, 为患者带来更大的益处。

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■名词解释

早期食管癌: 病灶局限于黏膜层和黏膜下层, 不伴有淋巴结转移的食管癌; 食管的癌前病变: 业已证实与食管癌发生密切相关的病理变化, 主要包括鳞状上皮不典型增生等。

■ 同行评价

本文对ESD技术在食管早癌和癌前病变的应用现状及技术方法做了相关介绍, 对该项技术的普及多有裨益, 有助于初中级内镜医师对该项技术的学习了解。

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