

胃黏膜下肿瘤微创治疗的进展

孙美玲, 刘冰熔

背景资料

黏膜下肿瘤分为恶性肿瘤及良性肿瘤。最值得讨论的胃黏膜下肿瘤为间质瘤, 因其为胃肠道最常见的间质性肿瘤。间质瘤的大小、部位及高倍镜视野下有丝分裂像影响切除的预后。由于胃肠道间质瘤存在潜在恶性的可能, 治疗局限胃间质瘤的主要目标是达到边缘阴性的切除, 这是一种获得完全治疗的有效方法。

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Minimally invasive surgeries for submucosal tumors of the stomach

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Abstract

Submucosal tumors (SMTs) of the gastrointestinal tract, which may be an occasional finding on routine upper gastrointestinal (GI) endoscopy, represent a diagnostic and therapeutic challenge. Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and have the potential to progress to malignancy. The primary treatment goal for localized GISTs is surgical resection with achievement of a negative margin (R0 resection). This is the effective way to achieve complete

treatment. Minimally invasive surgery has become common in the surgical resection of gastrointestinal SMTs. Recent advances in endoscopic technology provide various treatment modalities for gastric SMTs. Moreover, investigators have developed laparoscopic and endoscopic cooperative procedures. In addition, robotic surgery for SMTs is another choice. The purpose of this article is to review recent trends in minimally invasive surgery for gastric SMTs.

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Key Words: Minimally invasive surgery; Submucosal tumor; Endoscopic procedure; Robot; Laparoscopic and endoscopic cooperative procedure

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摘要

胃黏膜下肿瘤经常于胃镜检查中被发现, 给诊断及治疗带来了挑战。最值得讨论的胃黏膜下肿瘤为间质瘤, 因其为胃肠道最常见的间质性肿瘤。由于胃肠道间质瘤存在潜在恶性的可能, 治疗局限胃间质瘤的主要目标是达到边缘阴性的切除, 这是一种获得完全治疗的有效方法。微创治疗已经广泛应用在切除胃肠道黏膜下肿瘤方面。随着内镜技术的迅猛发展, 内镜下切除为胃黏膜下肿瘤的治疗提供了不同的方案。有些专家还提出了内镜与腔镜的联合治疗。除此以外, 机器人切除黏膜下肿瘤也成为可能。本文主要介绍微

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创治疗胃黏膜下肿瘤的进展.

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关键词: 微创治疗; 黏膜下肿瘤; 内镜切除; 机器人; 腹腔镜和内镜联合治疗

核心提示: 胃黏膜下肿瘤经常于胃镜检查中被发现, 给诊断及治疗带来了挑战. 胃黏膜下肿瘤为间质瘤因其为胃肠道最常见的间质性肿瘤且存在潜在恶性的可能. 治疗的主要目标是达到边缘阴性的切除. 微创治疗已经广泛应用在切除胃肠道黏膜下肿瘤方面. 随着内镜技术的迅猛发展, 内镜下切除为胃黏膜下肿瘤的治疗提供了不同的方案.

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0 引言

胃黏膜下肿瘤经常于胃镜检查中被发现, 给诊断及治疗带来了挑战. 黏膜下肿瘤分为恶性肿瘤及良性肿瘤. 恶性肿瘤如胃肠道间质瘤、恶性淋巴瘤、类癌及胃癌, 良性肿瘤如平滑肌瘤、异位胰腺及脂肪瘤等^[1]. 最值得讨论的胃黏膜下肿瘤为间质瘤, 因其为胃肠道最常见的间质性肿瘤^[2]. 胃肠道间质瘤起源于间质中的Cajal细胞^[2], 最常见于胃, 约占55%-60%, 小肠约占30%, 十二指肠约占5%, 结直肠约占5%^[3]. 间质瘤的大小、部位及高倍镜视野下有丝分裂像影响切除的预后^[4]. 由于胃肠道间质瘤存在潜在恶性的可能, 治疗局限胃间质瘤的主要目标是达到边缘阴性的切除, 这是一种获得完全治疗的有效方法^[5]. 这主要是因为其不侵及胃壁, 不需要广泛切除, 而且较少累计淋巴结, 不需要淋巴结清扫^[2]. 目前为止, 诊断及治疗黏膜下肿瘤最主要的方式是完全切除, 微创治疗已经广泛应用在切除胃肠道黏膜下肿瘤方面. 随着内镜技术的迅猛发展, 内镜下切除为胃黏膜下肿瘤的治疗提供了不同的方案. 有些专家还提出了内镜与腔镜的联合治疗. 除此以外, 机器人切除黏膜下肿瘤也成为可能. 本文主要介绍微创治疗胃黏膜下肿瘤的进展.

1 内镜下治疗

最近随着内镜进展, 出现了多种形式的内镜

切除术(endoscopic resection, ER), 包括标准圈套器息肉切除术^[6]、用生理盐水和圈套器的剥离活检术^[7]、用结扎装置的内镜黏膜下切除术(endoscopic submucosal resection with ligation device, ESMR-L)^[8]、用透明帽的内镜黏膜下肿瘤切除术(endoscopic submucosal tumor resection with a transparent cap, ESMR-C)^[9]、去顶术^[10]、用圈套器或切割器的内镜摘除术^[6]、用IT电凝刀的内镜摘除术^[11]、内镜黏膜下层剥离术(endoscopic submucosal dissection, ESD)^[12]、内镜下固有肌层剥离术(endoscopic muscularis dissection, EMD)^[13]、黏膜下隧道内镜肿瘤切除术(submucosal tunneling endoscopic resection, STER)^[14]、黏膜下内镜肿瘤切除术(submucosal endoscopic tumor resection, SET)^[15]、内镜黏膜下隧道切除术(endoscopic submucosal tunnel dissection, ESTD)^[16]、经隧道内镜固有肌层剥离术(tunneling endoscopic muscularis dissection, tEMD)^[17]、内镜下全层切除术(endoscopic full-thickness resection, EFTR)^[18].

1.1 早期ER 标准圈套器息肉切除术、用生理盐水和圈套器的剥离活检、ESMR-L、ESMR-C、去顶术仅适用于小的黏膜下肿瘤(直径<2 cm)^[19]. 需要指出的是去顶术经常用于黏膜下肿瘤的活检^[20]. 针对其治疗目的, 去顶术仅用于治疗脂肪瘤及囊性淋巴管瘤, 这是因为他们是良性肿瘤且能自行溶解. 虽然Fukuda等^[10]报道去顶术成功地切除胃体后壁大的脂肪瘤(5 cm×3 cm), 但我们仍需要仔细评估是否该术式适合黏膜下肿瘤的治疗. ESMR-C中提及的透明帽在内镜中得到广泛应用. 刘素芹等^[21]提出透明帽不仅可以用于内镜下黏膜切除术(endoscopic mucosal resection, EMR)中, 也可以用于ESD中. 透明帽可以起到支撑作用, 使得黏膜与黏膜下层之间留有一定空隙, 从而保持整个操作过程视野清晰^[22], 然后将电刀放置于该空隙进行操作, 可以更好的剥离病变组织, 减少并发症的发生.

1.2 ESD ESD作为一种新型的内镜治疗方法从EMR发展而来, 被广泛认可用于表浅胃肠道肿瘤的治疗^[23]. 近几年随着ESD技术进一步提高, 已用于深及黏膜下层病变的治疗, 如胃黏膜下肿瘤及胃癌. 标准ESD技术涉及病变周围环形切除及黏膜下层的剥离. 直视下直接剥离肿瘤

□ 研发前沿

本文主要介绍微创治疗胃黏膜下肿瘤的进展. 微创治疗已经广泛应用在切除胃肠道黏膜下肿瘤方面. 随着内镜技术的迅猛发展, 内镜下切除为胃黏膜下肿瘤的治疗提供了不同的方案. 有些专家还提出了内镜与腔镜的联合治疗. 除此以外, 机器人切除黏膜下肿瘤也成为可能.

□ 相关报道
 黏膜下内镜肿瘤切除术(submucosal endoscopic tumor resection, SET)、内镜黏膜下隧道切除术(endoscopic submucosal tunnel dissection, ESTD)、黏膜下隧道内镜肿瘤切除术(submucosal tunneling endoscopic resection, STER)及经隧道内镜固有肌层剥离术(tunneling endoscopic muscularis dissection, tEMD)最大的优点是在完整切除黏膜下肿瘤的同时保证消化系黏膜的完整性,降低了术后消化系发生渗漏及继发感染的风险。对于食管及贲门<3 cm黏膜下肿瘤,可考虑应用tEMD,尽管术后患者可能会出现皮下气肿、气胸等并发症,但均在保守治疗后得到改善。

以下的黏膜下层可以达到完整的切除并保证样本的完整性^[24]。不仅如此,还可以得到准确的组织病理分型^[25],尤其对于有症状且起源于黏膜下层的黏膜下肿瘤,ESD是较好的治疗方案^[1]。对于起源于或侵及固有肌层的胃黏膜下肿瘤,用标准ESD术完整安全的切除似乎并不可能。考虑到后续的剥离深及固有肌层,故应该仔细剥离肿瘤下的固有肌层。有研究^[26,27]报道ESD用于起源于固有肌层的黏膜下肿瘤的切除,完整切除率为64%-74.3%。但是最近有个关于143例黏膜下肿瘤切除的报道,肿瘤均在胃食管交界处且起源于固有肌层的,完整切除率为94.4%^[12]。其中有126例患者接受标准ESD术,并达到完整切除。考虑到上述报道的安全性及有效性,即使对于起源于固有肌层胃黏膜下肿瘤,标准ESD术也可以作为可考虑的治疗方案。而对于有较高风险穿孔的肿瘤,如肿瘤较大、广基或突出于腔外,均不考虑行标准ESD术^[12]。

1.3 EMD 正如上述描述的那样,对于起源于固有肌层的胃黏膜下肿瘤,内镜下切除需要剥离肿瘤周围的固有肌层。因此这个治疗过程不再称为ESD, Liu等^[13]命名为EMD,不同于ESD的情况如下: (1)用圈套器切除覆盖在病变上的黏膜层或者用纵型切口代替环形切口; (2)用电切结合钝性分离的方法将病变从黏膜下层及固有肌层完整剥离; (3)用钛夹闭合黏膜层^[13]。在31例起源于固有肌层的黏膜下肿瘤中,其中有30例肿瘤被完整切除,有4例发生穿孔,完整切除率达97%,穿孔率达13%^[13]。穿孔的患者均在保守治疗的情况下成功闭合。尽管穿孔率相对较高,但是其纵型切口省时且减少黏膜损伤,同时有利于钛夹闭合黏膜层。

1.4 黏膜下隧道术 在2010年, Inoue等^[28]报道了经口内镜下环形肌切开术(peroral endoscopic myotomy, POEM),即内镜下形成黏膜下隧道并切开食管环形肌治疗贲门失弛缓。在POEM术基础上, 2011年徐美东等^[14]首次报道STER治疗上消化道黏膜下肿瘤。STER治疗方法如下: (1)内镜寻找到肿瘤,并准确定位; (2)选择距离黏膜下肿瘤(submucosal tumors, SMTs)近口侧直线距离5 cm处食管或胃黏膜作为切口建立黏膜下隧道,显露肿瘤; (3)胃镜直视下完整切除肿瘤; (4)缝合黏膜切口。STER成功切除26例来源于固有肌层的上消化道SMTs,完

整切除率达100%。Inoue等^[15]又报道了SET用于食管及贲门的黏膜下肿瘤。除此以外, Gong等^[16]行ESTD切除起源于固有肌层的食管及贲门黏膜下肿瘤。SET和ESTD过程与STER类似。以上3种术式最大的优点是在完整切除黏膜下肿瘤的同时保证消化系黏膜的完整性,降低了术后消化系发生渗漏及继发感染的风险^[12]。对于食管及贲门起源于固有肌层的黏膜下肿瘤,可优先考虑SET及ESTD术式。此后, Liu等^[17]提出tEMD切除起源于固有肌层的食管及贲门上皮下肿瘤。当病变侵及固有肌层深层时应用EMD会伴随有高风险的穿孔、慢性瘘管形成及继发感染^[17],于是在此基础上Liu等^[17]提出tEMD。尽管术后患者可能会出现皮下气肿、气胸等并发症,但均在保守治疗后得到改善。对于食管及贲门<3 cm黏膜下肿瘤,可考虑应用tEMD。

1.5 EFTR Suzuki等^[29]在2001年首次报道用圈套器内镜下全层切除胃壁^[29],但此种方法不能用于完整切除>15 mm的病变。Ikeda等^[30]已经报道了用ESD的EFTR。此种术式扩大经自然腔道的内镜下治疗(natural orifice transluminal endoscopic surgery, NOTES)的潜在适应症。2011年, Zhou等^[18]用EFTR切除26例起源于固有肌层的胃黏膜下肿瘤。EFTR起源于ESD并包括4步: (1)深及固有肌层环形切除病变周围组织; (2)切入病变周围浆膜层造成活动性穿孔; (3)用圈套器切除病变及其周围的固有肌层和浆膜层; (4)用金属夹闭合胃壁缺口^[16]。EFTR虽为胃黏膜下肿瘤提供有效、安全、微创的治疗,但这需要先进的胃镜技术,尤其是胃镜下应用金属夹闭合穿孔创面。而且为证明此种术式切除肿瘤的可行性及有效性,仍需要来自多中心机构的进一步研究。2014年, Schmidt等^[31]报道了用缝合装置的EFTR。在黏膜下肿瘤底部用缝合装置形成浆膜层与浆膜层的缝合,然后用圈套器切除缝合处以上的肿瘤。此种术式有如下优点: (1)可用于接近4 cm的肿瘤切除; (2)可用于胃任意部位的黏膜下肿瘤切除; (3)对于潜在恶性的肿瘤,与浅层切除及ESD相比,此术式能够提供更充分的治疗^[31]。然而对于4 cm以上的黏膜下肿瘤或腔外生长的病变,无法内镜下切除。因为无法于肿瘤底部形成安全缝合,同时穿孔及不完全切除的风险也较高。

2 腹腔镜手术

很多研究^[32,33]对比腹腔镜治疗与开放手术治疗黏膜下肿瘤, 提出腹腔镜治疗的优点: 疼痛轻、炎症反应小, 失血量少, 术后进食早, 住院时间短。然而, 用腹腔镜治疗黏膜下肿瘤仍有许多问题需要考虑。2011年美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)指南^[34]及日本胃肠道间质瘤临床操作指南^[35]建议 ≤ 5 cm肿瘤腹腔镜切除是安全的, 对于 >5 cm胃肠道间质瘤腹腔镜切除的可行性及安全性仍不明确。但是仍有一些研究人员报道了腹腔镜切除较大的肿瘤(>5 cm, <10 cm)也是可行的^[32,36]。Hirano等^[37]报道了首例单孔腹腔镜术切除胃间质瘤, 需在脐部形成一个25 mm切口, 同时还需要一个2 mm的额外切口, 此种方法的优点是达到美观效果, 同时降低了出血、切口疝及器官损害的风险, 缺点是影响操作及操作角度变小增加了技术的复杂性。Sasaki等^[38]报道了用单孔腹腔镜术切除胃黏膜下肿瘤的临床经验, 但是用的仅仅是传统的腹腔镜器械, 所以为了更好地应用此技术需要改进器械。Henckens等^[39]报道了用双曲仪器采用单孔腹腔镜技术切除胃后壁的肿瘤, 双曲仪器有两个固定的弯曲, 使术者操作起来更加自然, 对于切除位于贲门或者幽门的病变仍较困难。目前仍需要发明更创新的仪器克服减孔治疗带来的困难。

3 内镜与腹腔镜联合治疗

Izumi等^[40]首次报道了用内镜及腹腔镜移除食管黏膜下肿瘤, 用内镜将肿瘤推出并用腹腔镜将其摘除。最近, Hiki等^[41]也报道了运用ESD成功协助腹腔镜局部切除胃间质瘤。这项技术被称作腹腔镜与内镜联合术(laparoscopic and endoscopic cooperative surgery, LECS), 即内镜下行ESD并用腹腔镜将肿瘤剥离后用缝合装置切除肿瘤的同时闭合创面。Tsujimoto等^[42]也证实了LECS治疗胃黏膜下肿瘤的可行性并达到令人满意的预后。与传统腹腔镜用线性缝合器的楔形切除相比, LECS的主要优势是减少了胃壁切除面积。腹腔镜辅助的内镜下全层切除术(laparoscopic assisted endoscopic full-thickness resection, LAEFR), 作为腹腔镜与内镜联合术的改进术式, 也可用于胃黏膜下肿瘤的治疗^[43]。包括4个主要过程: (1)用ESD环形切至病变周围的黏膜下层; (2)在腹腔镜的辅助下, 用EFTR从肌层全层切至浆膜层3/4或

2/3周; (3)用腹腔镜于腹腔侧将剩下的1/4或1/3全层切除; (4)用间断缝合或连续缝合闭合创面。与LECS相比, LAEFR包括EFTR以及代替线性缝合器的腹腔镜下缝合。对于LECS和LAEFR, 起源于固有肌层的腔内生长型胃黏膜下肿瘤是最好的适应症。

4 机器人治疗

最初用于胸心外科微血管切开的达芬奇手术系统目前一直用于腹腔手术, 有文章报道了其用于黏膜下肿瘤切除的疗效^[44,45]。Moriyama等^[45]表明达芬奇手术系统为外科医生的手及器械提供更自然的界面, 这些特点能更精确的切除肿瘤, 保证合适的切缘并准确缝合。此外, 对于位于贲门或者幽门较大的黏膜下肿瘤, 机器人治疗可以完成楔形切除并保留贲门或幽门^[44]。但是此种优势并不十分明确^[2], 有经验的外科医生亦可以通过传统腹腔镜达到准确的切除^[46]。此外, 联合治疗也可以达到以上效果。可见评定机器人治疗准确的效果仍需要长期随访观察以及结合其他手术中心的经验, 并将其与传统术式进行比较。

5 结论

胃黏膜下肿瘤的患者无特殊临床表现, 经常于常规胃镜检查中被发现, 但其来源性质很难确定^[47]。超声胃镜可以了解病变起源及大小, 但无法准确判断其良恶性。对于高度怀疑的胃肠道间质瘤, 并不常规推荐应用超声引导活检术, 但仍有一些专家倾向于用此种方式获得样本行组织病理学诊断^[48]。一旦获取足够的样本, 免疫组织化学分析的准确率可高达80%-91%^[49-51]。但是用超声引导活检术获取样本, 不充分率高达33.3%^[52,53]。故行微创切除不仅可以得到完整的样本行组织病理分析明确诊断, 同时可以达到治疗的目的。由于胃肠道间质瘤存在潜在恶性的可能, 治疗局限胃间质瘤的主要目标是达到边缘阴性的切除, 这是一种获得完全治疗的有效方法。随着微创技术的发展, 黏膜下肿瘤的切除不仅保留胃正常的容积及功能, 而且大大提高患者生活质量。尤其是ESD、EMD、ESTD、STER、SET、tEMD、EFTR等内镜下治疗的发展, 即使对于较大的黏膜下肿瘤, 也可将其完整切除。对于手中及术后出现的出血、穿孔等并发症, 均可用内镜下电凝止血及金属夹夹闭创面等保守

创新盘点

本文着重列举了微创治疗黏膜下肿瘤的术式, 包括早期内镜切除术(endoscopic resection, ER), 内镜黏膜下层剥离术(endoscopic submucosal dissection, ESD), 内镜下固有肌层剥离术(endoscopic muscularis dissection, EMD), 黏膜下隧道术, 内镜下全层切除术(endoscopic full-thickness resection, EFTR), 腹腔镜手术, 内镜与腹腔镜联合治疗及机器人治疗。尤其是随着内镜技术的进展, 各种各样的内镜治疗为消化系统黏膜下肿瘤的患者提供了微创的治疗。

应用要点

微创治疗为消化系统黏膜下肿瘤的患者带来了福音, 在明确诊断及达到治疗目的的同时, 使得患者术后恢复快、疼痛轻、炎症反应小、失血量少、术后进食早、住院时间短。但是微创治疗黏膜下肿瘤的报道仅限于个案报道或小样本量、单中心的回顾性分析。因此, 仍需要进一步研究证实以上微创治疗黏膜下肿瘤的可行性, 尤其在安全、完全切除方面予以重视。

治疗的方法予以处理。除此以外对于 ≤ 5 cm肿瘤腹腔镜切除是安全的, 也有一些研究人员报道了腹腔镜切除较大的肿瘤(>5 cm, <10 cm)也是可行的。内镜与腹腔镜联合治疗及机器人治疗也用于胃黏膜下肿瘤。但是微创治疗黏膜下肿瘤的报道仅限于个案报道或小样本量、单中心的回顾性分析。因此, 仍需要进一步研究证实以上微创治疗黏膜下肿瘤的可行性, 尤其在安全、完全切除方面予以重视。

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■名词解释

黏膜下肿瘤: 分为恶性肿瘤及良性肿瘤。恶性肿瘤如胃肠道间质瘤、恶性淋巴瘤、类癌及胃癌。良性肿瘤如平滑肌瘤、异位胰腺及脂肪瘤等。胃肠道间质瘤起源于间质中的Cajal细胞, 最常见于胃, 约占55%-60%, 小肠约占30%, 十二指肠约占5%, 结肠约占5%。胃肠道间质瘤存在潜在恶性的可能。

同行评价

这是一篇有关胃黏膜下肿瘤微创治疗进展的综述, 总结了各种微创方法治疗黏膜下肿瘤, 有一定的前沿性, 内容全面丰富, 对临床有一定的指导意义。

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