

早期胃癌内镜治疗抉择与补救手术

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【摘要】 我国早期胃癌检出率呈现逐年上升的趋势, 基于循证医学证据的内镜治疗已成为早期胃癌的主要手段之一。根据内镜诊断、影像学诊断及病理学评估来选择适合内镜切除的早期胃癌, 但是内镜切除存在手术风险和相应的并发症, 包括胃穿孔、出血及肿瘤残留等。因此, 需要严格遵循早期胃癌内镜切除的手术适应证, 掌握内镜切除技术, 选择合理的内镜切除策略, 并制定内镜切除后肿瘤残留补救手术方案, 将提高早期胃癌治愈率及手术安全性。笔者查阅相关研究, 系统阐述早期胃癌内镜治疗抉择与补救手术。

【关键词】 胃肿瘤; 早期; 内镜切除术; 策略; 补救手术

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Strategy of endoscopic resection for early gastric cancer and salvage surgery

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【Abstract】 The detection rate of early gastric cancer in China shows an increasing trend year by year, and endoscopic treatment based on evidence-based medicine has become one of the major modalities for early gastric cancer. Endoscopic diagnosis, imaging diagnosis and pathological evaluation are applied to evaluate early gastric cancer which is suitable for endoscopic resection. However, endoscopic resection has surgical risks and relevant complications, including gastric perforation, hemorrhage, and tumor residuals. Therefore, it is necessary to strictly follow the surgical indications of endoscopic resection for early gastric cancer, master the endoscopic resection technique, choose a reasonable strategy of endoscopic resection, and draw up a protocol of salvage surgery for tumor residue after endoscopic resection, which will improve the curability and surgical safety for early gastric cancer. The authors consult relevant research and systematically elaborate on the strategy of endoscopic resection for early gastric cancer and salvage surgery.

【Key words】 Stomach neoplasms; Early; Endoscopic resection; Strategy; Salvage surgery

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在全世界尤其是日本和韩国,早期胃癌的检出率呈现上升趋势,我国部分经济发达地区也呈现类似情况^[1-12]。早期胃癌检出率的提升,使得胃癌的治疗模式也发生变化。内镜切除术已成为早期胃癌的主要治疗手段之一,其与传统的胃切除术及淋巴结清扫术的治疗效果相似,但创伤更小、成本效益比更高、术后患者具有更佳的生命质量^[13-15]。合理的眼镜治疗将改变早期胃癌的治疗结局,改善患者预后,反之则可能会增加治疗风险,如出血、穿孔、腹腔感染、肿瘤残留及肿瘤局部复发转移等。对于内镜治疗失败的患者可以及时采取再次内镜切除或者外科补救手术,来保证肿瘤学安全性并减少并发症的发生。因此,了解早期胃癌内镜治疗适应证和禁忌证,掌握内镜手术关键技术,同时做好补救手术预案,对提高早期胃癌的治疗效果具有重要意义。笔者查阅相关研究,系统阐述早期胃癌内镜治疗抉择与补救手术。

一、早期胃癌内镜治疗抉择

(一)适应证

早期胃癌行内镜黏膜下剥离术(endoscopic submucosal dissection, ESD)和内镜黏膜切除术(endoscopic mucosal resection, EMR)需要明确病灶的所在部位、大小、侵犯深度、表面有无溃疡或者溃疡瘢痕形成、肿瘤分化程度以及有无淋巴结转移等。因此,内镜诊断、病理学诊断及影像学诊断尤为重要。胃癌ESD或EMR前内镜诊断可提供内镜治疗适应证及确定水平切缘等有关信息^[16-17]。见图1,2。窄带成像放大内镜技术可观察胃黏膜颜色变化和形态变化,对于存在黏膜分界线的病灶,观察其内部的不规则微血管征象和不规则微表面结构模式可明确早期胃癌内镜形态学改变^[16,18]。结合内镜下醋酸-靛蓝胭脂红喷涂染色技术可进一步明确病灶

范围,也有研究通过人工智能计算机辅助诊断系统来提高早期胃癌病灶范围诊断的准确性^[19-25]。链接彩色成像技术同样是一种影像增强技术,其可以帮助明确活动性幽门螺杆菌感染、胃黏膜肠上皮化生及早期分化型胃癌的诊断^[26-28]。EUS结合CT断层扫描检查可提高病灶侵犯胃壁深度及胃周淋巴结转移诊断的灵敏度和特异度。对于符合内镜切除扩大适应证的未分化癌及不符合内镜切除适应证的无溃疡病灶(absence of ulceration or ulcer scar, ULO)的分化型癌,侵犯至黏膜下层 $\geq 500\ \mu\text{m}$ 即黏膜下层2(SM2)建议行EUS检查^[29-31]。此外,也有研究通过黏膜下注射0.9%氯化钠溶液后行EUS检查来帮助鉴别诊断早期胃癌分期^[32]。

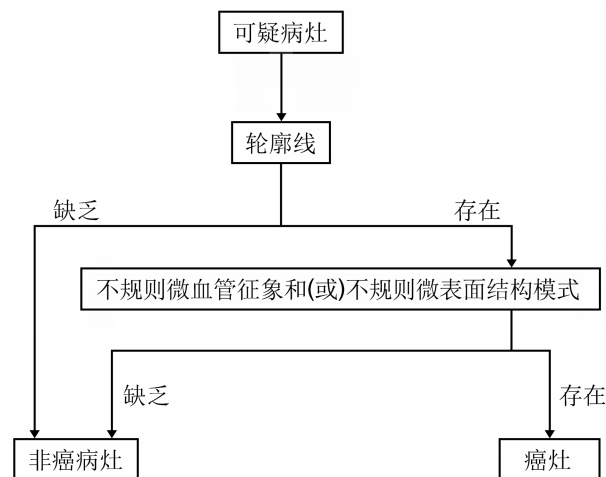


图1 放大内镜模式胃癌简易诊断流程

Figure 1 Magnifying endoscopy simple diagnostic algorithm for gastric cancer

日本《早期胃癌内镜黏膜下切除术和黏膜切除术指南(第2版)》规定EMR或ESD的绝对适应证是临床确诊的分化型黏膜内癌(cT1a期),病灶长径 $\leq 2\text{ cm}$,无溃疡或者溃疡瘢痕形成^[33]。其包括:(1)无

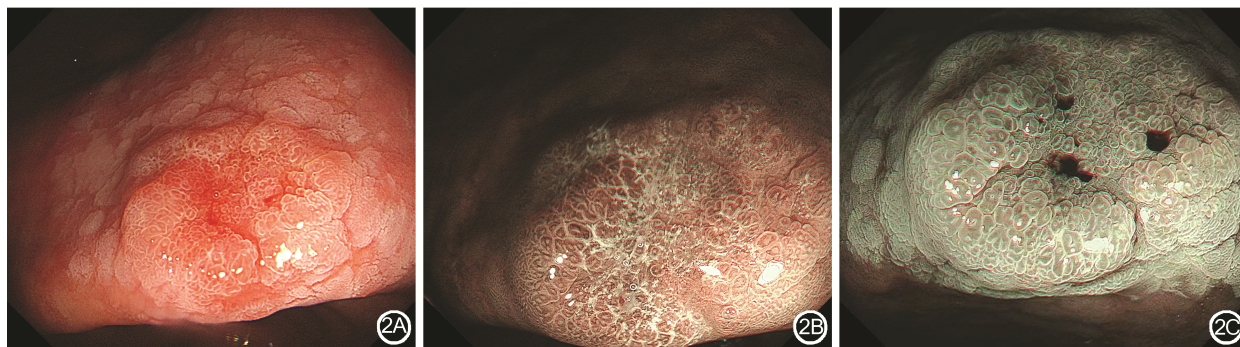


图2 内镜不同模式胃癌病灶结构显示 2A:白光模式;2B:放大内镜模式;2C:窄带成像模式

Figure 2 The structure of gastric cancer lesions with different endoscopic modes 2A: The white light mode; 2B: The magnifying endoscopy mode; 2C: The narrow-banding imaging mode

溃疡或者溃疡瘢痕(UL0型)的cT1a期分化型癌,病灶长径 >2 cm。(2)存在溃疡或者溃疡瘢痕型(UL1型)的cT1a期分化型癌,病灶长径 ≤ 3 cm。(3)无溃疡或者溃疡瘢痕(UL0型)的cT1a期末分化癌,病灶长径 ≤ 2 cm。上述内容参照日本JCOG0607及JCOG009/1010研究结果,证据级别为B级,推荐级别为强烈推荐^[34-37]。ESD扩大适应证主要被定义为预先设定的淋巴结转移率 $<1\%$ 的病灶,但是该定义尚无以5年生存率为研究终点的前瞻性验证性研究证实。随着ESD技术稳定性的持续增加,重复ESD的安全性和实用性不断提高。因此,符合上述绝对适应证的分化型癌初始行ESD或EMR后局部复发的黏膜内癌,且符合内镜治愈等级(endoscopic curability, eCura)为C-1级的病灶被认为是ESD的扩大适应证,其证据级别为C级,推荐级别为弱推荐^[38-39]。早期胃癌术前分期的诊断通常存在不确定性,尤其是组织病理学诊断为侵犯黏膜下层的病灶(pT1b期)。因此,部分不符合绝对适应证和扩大适应证的早期胃癌可以作为内镜治疗的相对适应证,如老年胃癌患者因体弱且合并症较多无法接受外科胃切除术时,也可以考虑行ESD^[40-42]。对于存在淋巴结转移风险,肿瘤侵犯固有肌层,ESD中抬举征阴性病灶,需慎重实施内镜切除。

(二)内镜治疗方法

内镜切除术的成功开展离不开内镜操作的各种设备及器械的研发和创新,尤其是各种黏膜切开刀(图3)在ESD中的应用^[43-47]。各种类型的头端带绝缘材料的IT刀,可以避免因刀头热损伤造成的穿孔和出血。通过体外内镜操作模拟训练、动物实验及内镜治疗操作培训,内镜医师可以逐渐掌握并安全实施ESD。Ono等^[48]报道头端绝缘的新型透热刀-2用于ESD,与传统的IT刀(IT-OM)比较,手术时间显著缩短。

符合ESD绝对适应证和扩大适应证的早期胃

癌行EMR不完整切除风险高,而ESD的整块切除率更高,所以ESD应取代EMR^[49-51]。理想的内镜治疗应考虑患者身体状况、病变特征、医疗机构的医疗环境、内镜医师的治疗经验及风险效益比等因素。内镜医师应充分履行告知义务,准确告知患者手术风险并征得患者充分理解后实施手术。在满意的麻醉状态下,明确病变部位和范围。标记病变范围,在黏膜下注射适量0.9%氯化钠溶液(100 mL 0.9%氯化钠溶液+2 mL 0.3%靛胭脂+0.2 mg肾上腺素)和透明质酸钠溶液1:1混合制成,可以使黏膜下层充分隆起(抬举征阳性)。采用Dual刀或者钩刀标记病灶并预切开黏膜,再使用IT刀或者其他能量设备沿着黏膜标记点外侧按照一定的顺序垂直靠近,轻轻按压刀头,并逐层切开黏膜层、黏膜下层,沿着固有肌层筋膜表面上方完整剥离病灶,遇到创面渗血或者小血管出血,冲洗创面干净后,可以采取电凝止血或者血管夹夹闭血管残端(图4A~4C)。不同部位的ESD操作技巧不同,需要反复实践掌握手术操作技巧,才能缩短手术时间。ESD中的剥离原则上应在反转操作下进行,在病灶肛侧制作黏膜瓣后夹闭带线组织夹并牵引病灶,可以获得良好的牵引效果,若反转操作困难时,也可以在顺镜下进行剥离操作。标本离体后应按照规定进行固定并拍照,由经验丰富的病理科医师对标本进行测量和取材,这对判断ESD手术切除疗效及预后评估至关重要(图4D~4F)^[52-53]。

JCOG0607研究结果显示:UL0型、肿瘤长径 >3 cm、肿瘤位于胃中部或上部、年龄 ≤ 60 岁是早期胃癌行ESD技术困难的独立危险因素^[54]。腹腔镜联合内镜手术(laparoscopic and endoscopic cooperative surgery, LECS)可以解决一些特殊部位操作困难的问题。LECS最早于2008年日本癌研有明医院Hiki报道,用于治疗胃壁黏膜下间质瘤,尤其对于肿瘤毗邻食管胃结合部、幽门管或者胃后壁等特

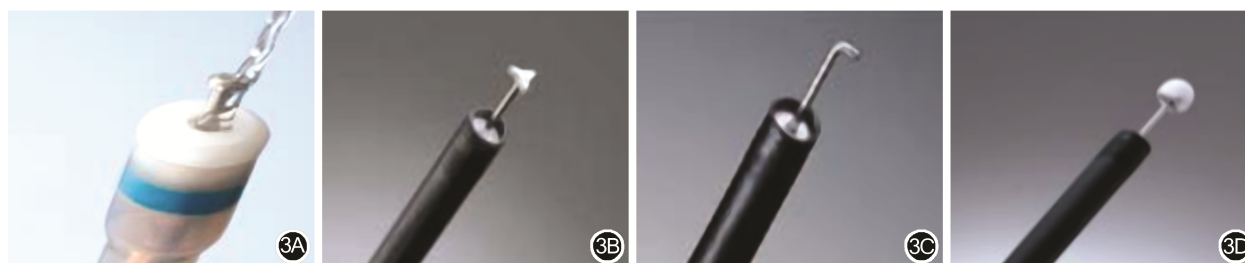


图3 各种类型的内镜黏膜切开刀 3A:两用刀;3B:三角刀;3C:钩刀;3D:绝缘刀

Figure 3 Different types of endoscopic submucosal dissection knives 3A: Dual knife; 3B: Triangle tip knife; 3C: Hook knife; 3D: Insulation-tipped diathermic knife

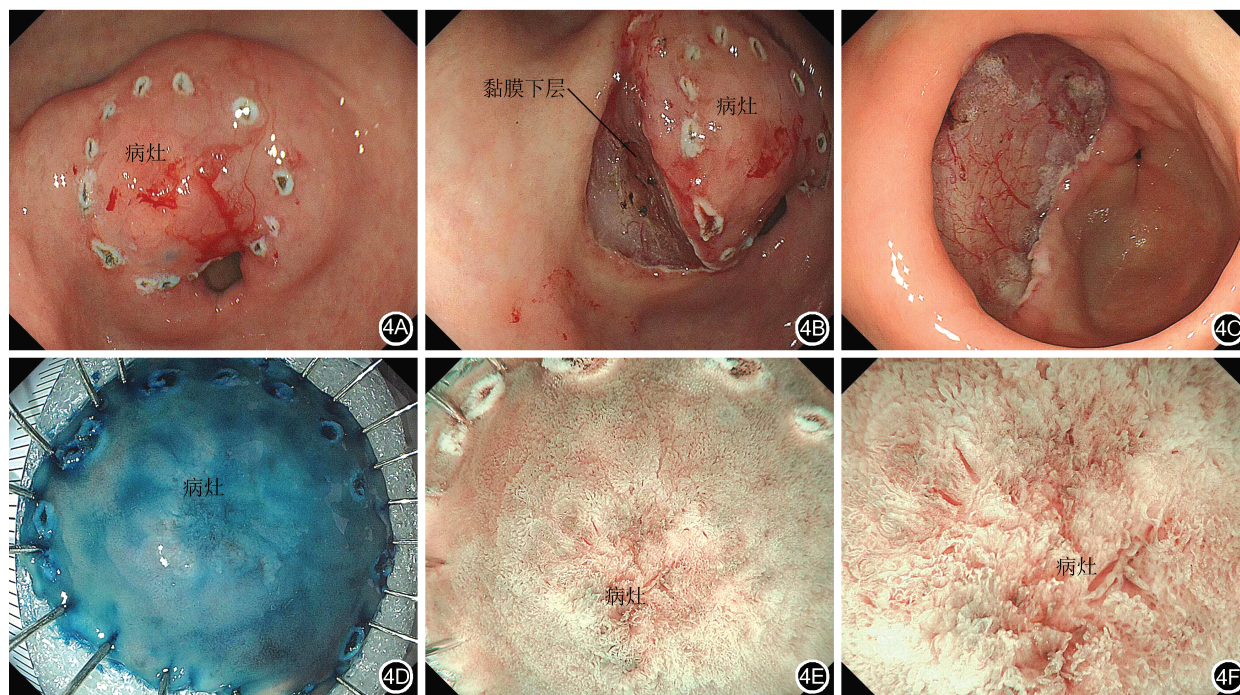


图 4 内镜黏膜下切除术手术操作过程、标本固定及观察 4A: 黏膜标记; 4B: 黏膜下层切开创面; 4C: 创面展示; 4D: 离体标本固定; 4E: 标本镜下观察(注水法); 4F: 标本镜下放大观察(注水法)

Figure 4 Endoscopic submucosal dissection (ESD) procedure, specimen fixation and observation 4A: Mucosa labeling; 4B: Submucosal incision; 4C: ESD wound demonstration; 4D: Specimen fixation; 4E: The specimen is observed under the microscope (water-filled method); 4F: The specimen is observed under microscopic magnification (water-filled method)

殊部位,开展LECS可以降低手术难度并增加手术安全性^[55-56]。腹腔镜是从胃壁浆膜面进行操作,很难确定胃腔内尤其是黏膜层及黏膜下层肿瘤位置及范围,此时由内镜经胃腔内精准定位肿瘤位置及边界,经黏膜面或者浆膜面切开胃壁,或者使用直线切割闭合器对肿瘤实施全层切除。LECS胃壁全层切除后创面呈线性愈合,而ESD手术创面呈人工溃疡面瘢痕愈合。笔者中心2016年起开展胃癌LECS,目前已积累较丰富的手术经验,并制订了详细的手术操作流程,包括患者体位和术者站位及内镜医师LECS标准化操作流程(图5),主刀医师立于患者左侧或两腿之间,扶镜手立于患者右侧,便于在单孔或者减孔腹腔镜下与内镜医师合作实施LECS。

LECS切开胃壁会增加腹腔污染风险,且有肿瘤种植和播散风险。非暴露胃壁全层切除技术可以解决上述难题,如非暴露技术双镜联合肿瘤手术、非暴露内镜下胃壁反转手术等^[57-61]。

(三) 内镜治疗的并发症

内镜手术(ESD或EMR)除了严格掌握适应证以外,还需要关注手术并发症的风险。严重并发症包括肿瘤残存和肿瘤复发,及其他不可预测风险。

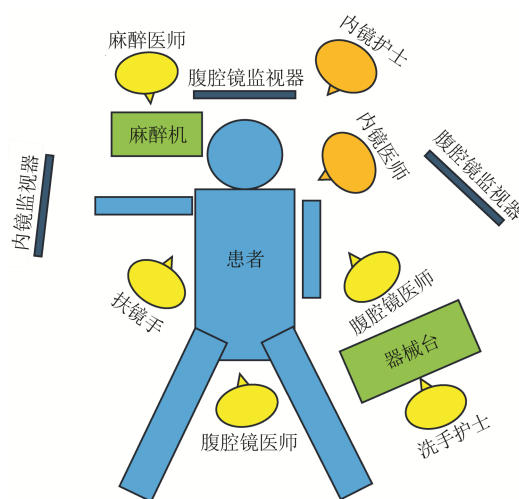


图 5 腹腔镜联合内镜手术患者体位、内镜医师及外科医师站位示意图(青海大学附属医院模式)

Figure 5 Illustration of patient's position, endoscopist and surgeon's standing position in laparoscopic and endoscopic cooperative surgery (Qinghai University Affiliated Hospital model)

常见并发症包括出血和穿孔。1项多中心前瞻性研究纳入约10 000例患者,结果显示:内镜手术并发症包括术后出血(4.4%)、输血(0.7%)、术中穿孔(2.3%)、延迟穿孔(0.4%)和并发症紧急手术(0.2%)

等^[62]。其他发生率较低的并发症包括胃腔狭窄(尤其病灶位于食管胃结合部和幽门管处)、肺炎和空气栓塞等亦值得关注^[63-64]。笔者认为:对早期胃癌开展ESD或EMR治疗时,应始终牢记并发症的风险,术前制订好预案和补救措施,尽可能避免发生并发症,一旦发生并发症时要作出及时的诊断及处理。此外,掌握娴熟的内镜治疗技术并积累一定数量的内镜治疗经验亦是保障手术顺利完成的关键。

1. 术后出血。应对切除后溃疡表面可见的残余血管采取适当的预防措施。有研究结果显示:使用止血钳或其他器械凝固切除后溃疡表面的可见残余血管可使ESD后出血率从7.1%下降至3.1%^[65]。内镜下创面止血的过程中要注意顺序,可以选择左右或者顺时针、逆时针进行,不要遗漏任何可能出血的地方。细血管可以用止血钳尖端点凝,大血管使用夹闭止血。创面底部更容易出现迟发性出血,采用止血夹进行止血。迟发性出血主要与病变位置、性质和切除大小有关。过度凝固血管会导致局部组织缺血,继而增加延迟穿孔的风险,因此,需要谨慎处理。ESD或EMR后应服用胃酸分泌抑制剂。1项RCT结果显示:在预防术后出血方面,质子泵抑制剂比H₂受体拮抗剂更有效^[66]。1项荟萃分析结果也得出类似结果^[67]。从预防术后出血的角度来看,ESD或EMR后进行二次内镜检查没有必要。日本的1项RCT结果显示:在没有使用抗血栓药物治疗的一般风险患者中,与未实施二次内镜镜检查组比较,实施二次内镜镜检查组在预防ESD后出血方面并无优势^[68]。1项荟萃分析也得出类似的结果^[69]。

2. 穿孔。ESD或EMR过程中发生穿孔,应首先考虑行内镜下闭合术。如果内镜夹闭成功,患者可通过禁食和使用鼻胃管进行保守治疗,同时给予抗菌药物治疗。保守治疗和仔细随访通常都能取得成功。如果穿孔无法闭合,或尽管穿孔表面闭合,但怀疑有腹膜炎,则应考虑外科急诊手术治疗,在腹腔镜下完成穿孔修补术。笔者单位常采取单孔或者减孔腹腔镜手术来完成上述操作。

二、早期胃癌内镜治疗后补救手术

约20%的分化型早期胃癌病变边界不明确,包括颜色正常、扁平型(0-IIb型)肿瘤长径≥21 mm、溃疡发现和黏膜表面分化不良的腺癌成分等因素会导致边缘难以确定,从而增加内镜切除术的手术风险。在内镜切除过程中内镜医师应仔细评估病灶边缘,同时考虑边缘不清晰等因素。当内镜医师无

法判断病灶边缘时,需谨慎开展内镜切除术。因此,非治愈性内镜手术会造成肿瘤残留并增加肿瘤复发转移风险,制订内镜治疗失败后的补救手术预案具有重要意义。

(一)内镜治疗后补救手术适应证

目前,符合内镜切除适应证的早期胃癌手术疗效评价按照eCura评分系统进行评价,内镜切除疗效评价基于局部因素及淋巴结转移风险,分为eCura A级、B级和C级。是否需要行外科补救手术,需要根据eCura评分系统评价结果确定。内镜切除疗效eCura A级为治愈性切除,肿瘤被整块切除并满足以下3种类型之一:(1)无论病灶大小,主要成分为分化型癌,病理学分期为pT1a期、病灶无溃疡或溃疡瘢痕形成(UL0)、水平切缘阴性(HM0)、垂直切缘阴性(VM0)、淋巴浸润阴性(Ly0)、脉管侵犯阴性(V0)。(2)肿瘤长径≤2 cm,主要成分为未分化型癌,病理学分期为pT1a期、病灶无溃疡或溃疡瘢痕形成(UL0)、水平切缘阴性(HM0)、垂直切缘阴性(VM0)、淋巴浸润阴性(Ly0)、脉管侵犯阴性(V0)。(3)肿瘤长径≤3 cm,主要成分为分化型癌,病理学分期为pT1a期、存在溃疡或者溃疡瘢痕(UL1)、水平切缘阴性(HM0)、垂直切缘阴性(VM0)、淋巴浸润阴性(Ly0)、脉管侵犯阴性(V0)^[70-71]。eCura B级为病灶被整块切除,肿瘤长径≤3 cm,主要成分为分化型癌,并且满足下列标准:病理学分期为pT1b1期(即病灶在黏膜固有肌层内<500 μm, SM1),水平切缘阴性(HM0)、垂直切缘阴性(VM0)、淋巴浸润阴性(Ly0)、脉管侵犯阴性(V0)。eCura C级为非治愈性切除,即可能存在肿瘤残留。当eCura C级病变为分化型病变,并且不符合eCura A、B级标准,可被归类为eCura C级,但未作整块切除或有阳性水平边缘时,则被视为eCura C-1级。其他eCura C级病变均被视为eCura C-2级,包括分化型癌中有未分化成分、肿瘤长径>2 cm。

对于转移风险低的eCura C-1级病灶,除了开展外科补救手术以外,还可根据医疗机构的诊疗规范及流程,在患者知情同意的情况下,再次行ESD、透热疗法或随访。通常情况下,开放或者腹腔镜补救手术切除适合下列患者:(1)肿瘤长径≤3 cm,主要成分为分化型癌,病理学分期为pT1a期和存在溃疡或者溃疡瘢痕(UL1)。(2)肿瘤长径≤3 cm,主要成分为分化型癌,并且病理学分期为pT1ba期(SM1)病灶。对于eCura C-2级病灶,考虑到转移及复发风险高,尤其是经内镜确定的残余病灶加上切

除标本总长径 >3 cm,以及黏膜下病灶浸润部分被零星切除或者判定切缘阳性的患者,应积极进行ESD后的开腹或者腹腔镜补救手术。对于ESD后疗效评价为eCure C级病灶,在获得患者的知情同意后,应向其解释复发患者治愈的可能性很低。1项纳入1 101例胃癌ESD后行开腹或腹腔镜手术切除患者的研究结果显示:淋巴结转移风险评估可通过eCure风险评分系统进行分层分析,总分为7分,即肿瘤长径 >3 cm为1分,肿瘤浸润深度为病理学分期pT1b2期(SM2)为1分,淋巴浸润阳性为3分,脉管浸润阳性为1分,垂直切缘阳性为1分。其中,0~1分为低风险组,2~4分为中风险组,5~7分为高风险组。见图6^[72]。

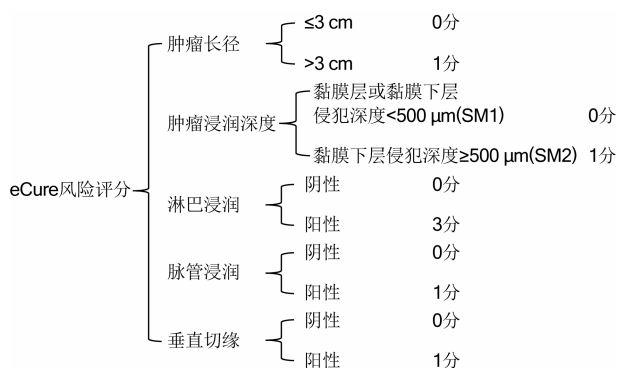


图6 内镜手术切除后淋巴结转移风险eCure评分系统

Figure 6 eCure scoring system for risk of lymph node metastasis after endoscopic resection

(二)补救手术方式

内镜治疗后补救手术以腹腔镜手术为主,发生出血或穿孔引起的腹膜炎等并发症需行急诊腹腔镜手术^[73]。内镜切除疗效评价为eCure C-1级及eCure C-2级外科补救手术主要采取腹腔镜保功能手术,包括腹腔镜局部扩大切除术+前哨淋巴结活组织检查术、腹腔镜胃癌根治术、D₁或D₁₊淋巴结清扫术、保留幽门的远端胃癌根治术、近端胃切除术等。

虽然患者行ESD或EMR后造成胃壁水肿、纤维化,局部淋巴引流网络异常,给手术带来困难,但已有的研究结果显示:非治愈性ESD后附加治愈性胃切除术在手术安全性和肿瘤安全性方面与标准胃切除术比较,差异均无统计学意义^[74]。补救手术也可行LECS,如前所述,LECS可以实现非暴露的胃壁全层切除术,及前哨淋巴结活组织检查术。术前或者术中通过内镜在人工溃疡病灶周围注射纳米碳或者吲哚菁绿作为示踪剂来标记病灶和淋巴示踪,不仅可以对病灶进行精准定位而且可以明确局部淋巴引流范围,实现精准切除,同时术中对前

哨淋巴池切除行快速冷冻切片病理学检查以明确是否有淋巴结转移。若无阳性转移淋巴结,即可完成淋巴结清扫,术后密切随访观察。韩国的SENORITA研究结果显示:非治愈性ESD后荧光示踪前哨淋巴结导航手术可以避免不必要的额外胃切除术,提高患者的生命质量^[75-76]。内镜治疗疗效评价为eCure C-2级患者存在淋巴结转移高风险,补救手术若行腹腔镜胃癌根治术,需对胃周淋巴结进行D₁或D₁₊清扫术,以期达到R₀切除。目前尚没有高级别循证医学证据支持保留迷走神经的胃癌根治术会提高患者术后长期生命质量和营养状态,但部分回顾性研究及短期随访结果显示:其对于改善患者术后腹泻、减少胆石症的发生率及体质量的维持具有优势^[77-79]。

三、结语

随着我国早期胃癌检出率的提高,越来越多的早期胃癌患者会接受内镜治疗。笔者认为:胃癌内镜切除术存在一定风险,需谨慎开展内镜切除术,应严格掌握其适应证,避免盲目扩大适应证范围,积极开展内镜医师规范化诊断与治疗培训,包括内镜治疗动物实验和模块化操作培训课程等。此外,还应重视多学科资源整合,尤其是内镜与腹腔镜技术的结合,由此可以提高内镜治疗疗效,增加手术安全性同时降低手术风险,真正做到精准手术。早期胃癌内镜治疗还存在很多困难和不足,如术前如何提高胃癌的精准分期和精准定位,采用超高分辨率内镜,及电子放大技术和物理或化学染色技术,清晰呈现局部胃黏膜微观形态学变化,结合人工智能帮助医师实现精准诊断和精准治疗,由此既达到肿瘤的精准分期和彻底切除,又能够最大限度地保全功能,提高患者术后生命质量。

内镜手术还有以下局限性:(1)早期胃癌存在潜在淋巴结转移风险,异时性或同时性多源发癌极易漏诊,存在基底部及切缘肿瘤残留的风险。(2)ESD手术创面的人工瘢痕性愈合会造成胃壁运动功能异常,在特殊解剖部位如食管胃结合部及幽门管易发生变形等问题。此外,如何避免或降低ESD并发症风险亦是内镜医师关注的焦点问题之一。LECS是目前早期胃癌较好的治疗手段之一,加强内镜医师与外科医师的团结协助,整合各自优势,扬长避短,让患者受益是治疗的核心。LECS也存在不足,如何解决手术室内镜的清洗与消毒,如何优化内镜与腹腔镜操作流程,以及做好手术室医护配合,提高手术效率是亟需解决的问题。笔者认

为:积极开展多中心临床研究,提高内镜手术质量,降低手术风险,并制订符合我国国情的胃癌内镜治疗操作指南和外科补救手术方案是研究者的下一步工作。

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