

内镜治疗肝硬化患者上消化道早癌的风险及处理策略

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Risk associated with endoscopic treatment of early upper gastrointestinal cancer in patients with liver cirrhosis and management strategies

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Abstract

Patients with liver cirrhosis have an increased risk of upper gastrointestinal carcinomas, especially those with alcoholic cirrhosis. With the widespread use of endoscopic examination, more and more upper gastrointestinal carcinomas are found and treated at an early stage. Endoscopic resection is the first-line treatment for early upper gastrointestinal carcinomas. Patients with liver cirrhosis may have comorbid thrombocytopenia, coagulation dysfunction, gastroesophageal varices, *et al*, which may increase the risk of complications such as bleeding and infection. Recently, several studies concerning the efficacy and safety of endoscopic treatment of early esophageal/gastric cancer or precancerous lesions have been reported. In this review, we summarize the risk associated with endoscopic treatment of early upper gastrointestinal cancer in patients with liver cirrhosis and management strategies, aiming to providing useful tips for clinicians.

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Key Words: Early esophageal cancer; Early gastric cancer; Precancerous lesion; Liver cirrhosis; Endoscopic treatment; Gastroesophageal varices

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摘要

肝硬化患者患上消化道肿瘤风险增加, 尤其是酒精性肝硬化患者. 随着内镜检查的推广及普及, 越来越多的上消化道早癌得以早期发现及治疗. 内镜治疗已成为上消化道早癌的首选治疗方式, 肝硬化患者由于可能存在血小板减少、凝血功能障碍、合并食管胃静脉曲张等情况, 内镜治疗过程中出血、感染等风险较大. 近年来国内外已有部分研究探讨内镜治疗肝硬化伴上消化道早癌的安全性及有效性. 本文总结了近年来发表的内镜治疗肝硬化伴上消化道早癌的研究结果, 简要综述其风险及防治策略, 为临床提供指导.

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关键词: 早期食管癌; 早期胃癌; 癌前病变; 肝硬化; 内镜治疗; 食管胃静脉曲张

核心提要: 内镜治疗是上消化道早癌的首选治疗方式, 肝硬化患者由于可能存在血小板减少、凝血功能障碍、合并食管胃静脉曲张等情况, 内镜治疗风险较大. 本文简单总结肝硬化上消化道早癌患者内镜治疗的风险及防治策略.

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0 引言

食管癌及胃癌是最常见上消化道恶性肿瘤, 其发病率及死亡率分别居全球恶性肿瘤的第8位、第5位及第6位、第4位^[1]. 东亚国家如我国、韩国、日本食管癌及胃癌发病率较高, 在我国食管癌的发病率及死亡率居恶性肿瘤第6位及第5位, 胃癌发病率及死亡率均居恶性肿瘤第3位^[2]. 我国食管癌新发病例及死亡病例占全球总数的50%以上, 胃癌新发病例及死亡病例占全球总数40%以上^[1]. 即使接受了综合治疗(如手术、化疗、放疗、免疫治疗等), 进展期食管癌及胃癌的5年生存率仍低于30%, 而早期食管癌及胃癌切除后5年生存率在90%以上^[3,4]. 随着人民群众健康意识的提高、内镜筛查的普及以及精查技术的发展, 食管和胃早癌及癌前病变的检出率不断提高, 食管癌及胃癌整体死亡率不断下降^[5,6]. 食管/胃早癌及癌前病变的治疗主要包括内镜及外科手术治疗, 内镜治疗具有微创、经济、恢复快、术后生活质量高等优点, 且与外科手术相比, 二者术后无瘤生存率相近^[7-10]. 常用内镜治疗方法包括内镜下黏膜切除术(endoscopic mucosal resection, EMR)、内镜黏膜下剥离术

(endoscopic submucosal dissection, ESD)、内镜下病灶消融术等, 与其他内镜治疗方式相比, ESD具有高整块切除率、高治愈性切除率, 切除标本有利于病理评估等优点, 已成为食管/胃早癌及癌变病变的首选治疗方式^[11-15].

肝硬化是临床常见病、多发病, 居全球常见致死病因第11位, 年死亡人数约100万. 我国是肝硬化大国, 肝病患者约3亿, 肝硬化死亡人数占全球肝硬化死亡人数的11%^[16]. 由于有部分共同危险因素如饮酒、吸烟、肥胖等, 肝硬化患者患上消化道肿瘤风险增加, 研究显示^[17-19], 肝硬化患者患食管癌和胃癌的风险分别是无肝硬化患者的2.6倍及1.9倍. 然而肝硬化患者中食管/胃早癌及癌前病变的检出率目前尚无相关统计学资料. Zhu等^[20]发现食管早癌行隧道内镜黏膜剥离术的患者中4.24%(25/565)伴有肝硬化, 我们的研究发现因食管早癌/癌前病变行ESD治疗者中0.94%(1/106)合并肝硬化, 而因胃早癌/癌前病变行ESD治疗者中2.05%(7/342)合并肝硬化^[21]. 肝硬化合并上消化道早癌时内镜治疗既可以治疗食管胃静脉曲张(gastroesophageal varices, GOV), 减少GOV出血风险, 又可以切除上消化道早癌病变, 改善患者预后. 而且GOV及上消化道早癌治疗后均需要定期随访评估有无复发, 因此消化内镜在肝硬化合并上消化道早癌的治疗及随访中显得尤为重要. 肝硬化患者行内镜治疗的风险增加, 主要由于以下方面的原因: (1)凝血功能障碍、血小板减少、门脉高压性胃病等伴随情况增加术中及术后出血风险^[22]; (2)如早癌或癌前病变位于GOV表面或邻近GOV, 可增加术中、术后出血风险, 其GOV的内镜治疗史可导致黏膜下层纤维化, 增加ESD操作难度; (3)感染风险增加; (4)合并严重腹水、肝肺综合征、肝肾综合征等严重并发症时, 无法耐受手术等. 因此合理把握适应证、恰当的围手术期管理至关重要. 为此, 我们结合近年来发表的内镜治疗肝硬化伴上消化道早癌的研究结果及自己的临床经验, 简要综述肝硬化上消化道早癌患者内镜治疗的风险及防治策略, 为临床提供指导.

1 肝硬化患者上消化道早癌内镜治疗的安全性及有效性

近年来已有一些内镜治疗伴有肝硬化的上消化道早癌的临床研究(表1中总结了目前报道的样本量在5例及以上的研究结果).

从表中可看出, 此类患者内镜治疗的主流方法为ESD, 其他报道的方法包括EMR、经隧道黏膜剥离术(endoscopic submucosal tunnel dissection, ESTD)、射频消融、氩气电凝^[40]、套扎等. 文献报道的整块切除率为75%-100%, 治愈性切除率为62.5%-100%, 并发症最常见的为术中或术后出血. 复发概率各研究报道差异

表 1 内镜治疗肝硬化伴上消化道早癌及癌前病变的相关研究结果

研究者	发表年	病种及例数 ^a	酒精性肝硬化患者比例	内镜治疗方法	整块切除率	治愈性切除率	并发症	复发
Tan ^[21]	2023	1食管, 7胃	12.5%(1/8)	ESD	75%	62.5%	4例术中出血、1例胸痛及发热	无
Simonnot ^[23]	2023	食管(112例患者, 134处病变)	64.2%(86/134)	ESD 101, EMR 30, RFA 3	86%	63%	3例穿孔、8例术后出血、8例脓毒血症、22例食管狭窄	17%
Zhang ^[24]	2023	15个患者, 16处病变(8食管, 8胃)	26.7%(4/15)	ESD	100%	100%	2例术后出血	6.7%
Zhu ^[20]	2022	25食管	52%(13/25)	ESTD	88%	76%	48%术中出血、8%术后出血、44%发热、8%肺炎、8%食管狭窄	4%
Kim ^[25]	2022	17胃	70%	ESD 15, EMR 2	94.1%	NA	2例出血	23.5%
Choi ^[26]	2022	食管(15例患者, 17处病变)	73.3%(11/15)	ESD	88.2%	82.4%	2例出血, 3例术后狭窄	20%(2/10)
程芮 ^[27]	2022	4食管, 6胃	/	ESD	100%	100%	1例GOV出血	无
Xu ^[28]	2019	6食管	66.7%(4/6)	ESD 5, RFA 1	100%	80%	2例术中出血、1例食管狭窄	无
Choi ^[29]	2018	158胃	31.6%(50/158)	ESD	96.8%	89.9%	5例术中出血, 11例术后出血, 3例穿孔	1例复发
Choe ^[30]	2018	43胃	/	ESD	97.7%	95.3%	4例术后出血, 2例穿孔	无
Wang ^[31]	2017	8例食管早癌	100%(8/8)	RFA	/	/	2例黏膜内血肿、1例黏膜裂伤	2例患者有残留, 接受第二次RFA
Tsou ^[32]	2016	食管(6例患者, 11处病变)	/	ESD	81.8%	77.8%	2例术中出血	无
Kato ^[33]	2015	69胃	23.2%(16/69)	ESD	99%	90%	4例术后出血, 2例穿孔	/
Palmer ^[34]	2015	8食管	37.5%(3/8)	EVL4; EVL+EMR4	/	/	无	无
Sawaguchi ^[35]	2014	7食管	85.7%(6/7)	ESD	100%	88.9%	无	无
Repici ^[36]	2012	5胃	/	ESD	100%	100%	2例术后出血	无
Choi ^[37]	2012	23胃	/	ESD	82.6%	82.6%	1例出血	无
Kwon ^[38]	2011	胃(18例患者, 22处病灶)	44.4%(8/18)	ESD 12, EMR 10	90.9%	86.4%	/	/
Ogura ^[39]	2008	胃(15例患者, 18处病灶)	/	ESD	88.9%	77.8%	3例术后出血	无

^a: 食管: 食管早癌或癌前病变; 胃: 胃早癌或癌前病变; /: 无相关数据. ESD: 内镜黏膜下剥离术; EMR: 内镜下黏膜切除术; EVL: 内镜下套扎术; RFA: 射频消融.

较大, 可能与纳入病人内镜治疗指征把握不严格有关, 部分研究有较高比例的患者存在黏膜下层侵犯, 甚至脉管浸润^[23,25,26].

2 食管胃静脉曲张的风险及处理策略

食管胃静脉曲张带来的风险主要是静脉曲张破裂出血.

因此对于伴有GOV的肝硬化患者, 在进行ESD治疗前需要考虑以下因素: GOV与病灶的关系、ESD术中GOV出血风险、先处理GOV等待过程中食管/胃病变浸润进展风险、内镜操作者经验等^[24]. 总体处置原则为: (1)GOV出血风险高, 早癌病变浸润风险低, 先处理GOV; (2)GOV出血风险和早癌病变浸润风险均高时, 先处理病变或同

期处理; (3)GOV出血风险低, 早癌病变浸润风险高, 先处理病变; (4)GOV出血风险和早癌病变浸润风险均低时, 处理病变或随访待定. GOV出血风险高低, 早癌病变浸润风险高低, 建议采用LDRf分型/Sarin分型、食管AB分型、早期胃癌VS分型、内镜下治疗适应症等来量化. 此外, 治疗顺序还跟GOV与上消化道早癌或癌前病变的位置关系有一定关系. 其位置关系可分为三种: 病变远离GOV, 病变紧邻GOV和病变位于GOV上. 当病变远离GOV时, 可按照上述总体原则进行治疗即可, 由于此种情况下理论上GOV的治疗对早癌病变的内镜治疗影响不大, 因此即使GOV出血风险较高, GOV和早癌病变的处理亦可同期进行. 如先行GOV治疗, 目前关于分期手术的合适间隔时间并没有相关指南, 仅少量个案或短篇报道, 大多是根据GOV内镜下治疗方案来选择早癌病变非同期治疗的合适时间, 文献报道最短间隔为3天, 多为GOV治疗2-4周内完成病变内镜切除. 如ESD与GOV同步处理时(尤其适用于病变浸润风险较高的患者), 应谨慎选择GOV治疗方法, 如需内镜切除病变位于GOV肛侧端且术后出血风险较高, 可能需要内镜下止血时, GOV治疗尽量不选择套扎治疗, 因再次进镜可能导致套扎环早期脱落引起GOV急性出血.

当病变紧邻GOV或位于GOV上时, 内镜治疗肿瘤病变可能导致GOV出血, 因此是否需要处理GOV、GOV处理时机及方法都需要仔细权衡. 此类患者如GOV出血风险较高, 而病变进展风险较低时, 建议先处理GOV; 如病变进展风险较高, 则先行病变处理或病变与GOV同时处理. GOV最佳处理方式仍有争议, 内镜及介入均可选择. 当病变位于食管静脉曲张上方时, 如果选择内镜治疗食管静脉曲张, 可选择硬化剂治疗; 如需选择EVL, 建议尽量避免套扎环累及病变边界或病灶, 应留有足够安全边界, 确保切除病灶标本完整, 尤其是病变>2 cm, 因其可影响后期病变病理评估^[24,41]. 有学者认为内镜治疗可能造成黏膜下纤维化, 增加后续内镜治疗病变的难度^[35,42], 由此推荐经颈静脉肝内门体分流术(TIPS)或球囊导管逆行性静脉栓塞术用于预防GOV出血^[23,28,43,44]. 然而也有报道直接行EVL、射频消融或外科手术、双镜联合同时治疗GOV和上消化道早癌/癌前病变^[31,34,45,46]. 目前有2篇专门针对伴GOV的上消化道早癌的临床研究. Zhang等^[24]报道了15例(共16处病变)伴GOV的患者, 其中2处病变位于GOV上, GOV和病变处理同时进行, GOV采用了套扎和组织胶注射; 6处病变紧邻GOV, 其中3处GOV未予处理, 1处与ESD同时进行, 另两处GOV先处理, ESD与GOV治疗后4、28天后进行. 另一项多中心研究纳入112例患者134处食管病变, 其中71例患者伴有食管静脉曲张: 为预防静脉曲张出血, 7例患者内镜切除术前

接受TIPS治疗, 8例患者术前接受套扎治疗, 15例患者接受生长抑素治疗, 9例患者内镜切除时同时行食管静脉曲张套扎治疗^[23]. 考虑到我国大部分单位介入治疗开展不够, 结合文献及我们自己经验, 我们认为内镜治疗静脉曲张是可行的, 可选择的方法包括套扎、硬化剂注射及组织胶注射(胃静脉曲张).

3 血小板减少及凝血功能异常的风险及处理策略

肝硬化患者因为脾功能亢进、凝血因子合成障碍可导致血小板减少及凝血功能异常, 此类患者行内镜治疗时出血风险增加^[22,47,48], 包括术中及术后出血, 因出血需要内镜下电凝等处理, 也可能增加穿孔的风险. 一项纳入10项研究3244例患者的Meta分析发现肝硬化患者EMR/ESD术中及术后出血率为9.5%(95%CI: 4.0-21.1), 穿孔率为6.6%(95%CI: 4.2-10.3), 肝硬化患者EMR/ESD术中出血率高于非肝硬化患者, 而其他并发症发生率与非肝硬化患者无统计学差异^[47]. 因此围手术期对血小板减少和凝血功能异常的处理至关重要, 然而血小板减少/凝血功能异常到何种程度需要处理目前仍缺乏统一共识. Repici等^[36]发现INR>1.33和/或血小板低于105000/mm³ ESD术中/后出血风险增加, 而另一些学组将INR>1.5和/或血小板低于50000/mm³作为肝硬化患者耐受侵入性手术的临界值^[22,49]. 而基础研究发现正常功能血小板计数在20000-30000/mm³即可产生足够凝血酶诱发正常凝血反应^[50]. Zhang等^[24]报道的15例患者中有一例患者血小板计数<30000/mm³, 经输注血小板后血小板计数>30000/mm³, 成功完成ESD治疗, 术中及术后无明显出血. 我们的研究中有2例患者有两例INR>1.33和PLT<50000/mm³的患者ESD术中出现出血^[21]. 因此我们建议INR>1.33的肝硬化患者围手术期输注冰冻血浆和/或冷沉淀, 建议输注至INR<1.33或ESD术后3天; 血小板计数<50000/mm³的患者建议输注血小板, 如血小板<30000/mm³的患者建议输注至血小板>30000/mm³再行内镜下治疗.

4 其他少见风险及处理策略

肝硬化患者伴发的其他可能影响内镜治疗决策的情况包括低蛋白血症、腹腔积液、肝肺综合征、肝肾综合征、原发性肝癌、感染、肝功能衰竭、肝性脑病等. 研究显示Child-Pugh C级或合并肝癌患者ESD治疗获益不大^[20,33]. 如肝硬化患者伴发肝肺综合征、肝肾综合征、肝性脑病、原发性肝癌、肝功能衰竭(Child-Pugh C级)、肝性脑病等严重影响患者预后的情况, 尤其是预期生存期不长时, 上消化道早癌或癌前病变的处理与否对患者生存期无影响, 不建议积极干预, 如患者及家属强烈要求干预, 应在上述疾病得到相对控制, 能够耐受内

镜手术及麻醉时, 在充分告知获益及风险后可考虑内镜治疗。伴发严重感染者尤其是肺部感染者, 应等感染控制后择期行内镜下治疗。大量腹腔积液严重者应先将控制至少-中量, 以减少术中腹腔积液对呼吸的影响及感染风险。低蛋白血症可能导致消化道黏膜水肿, 增加内镜治疗难度、穿孔风险、影响创面愈合, 因此血清白蛋白 <30 g/L者建议输注白蛋白。肝硬化患者如内镜治疗过程中存在出血、穿孔、固有肌层损伤等情况, 或伴有其他感染高风险情况(如低蛋白血症、中-大量腹腔积液、伴糖尿病等), 围手术期建议使用抗生素预防感染。

5 结论

肝硬化患者上消化道肿瘤风险增加, 因此肝硬化患者胃镜随访过程中应注意筛查上消化道肿瘤性病变及癌前病变。肝硬化患者内镜治疗上消化道早癌及癌前病变时出血、感染等风险增加, 因此围手术期处理至关重要。合理处理GOV、血小板减少、凝血功能异常、低蛋白血症、腹腔积液等伴随情况是保证内镜治疗安全有效的前提。

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• 消息 •

书 讯



本刊讯 由池肇春教授等主编的《代谢相关脂肪性肝病肝外并发症》已由天津科学技术出版社出版发行。

本书的出版为国内首创, 填补了国内有关这方面的空白, 拓宽了对《代谢相关脂肪性肝病》认识的高度和深度。《代谢相关脂肪性肝病肝外并发症》分总论和各论两部分。1-4章为总论, 分别介绍代谢相关脂肪性肝病肝外并发症研究现状与进展, 包括发病风险、发病机制和治疗近展; 脂肪代谢生物化学和分子生物学; 代谢相关脂肪性肝病肝外并发症免疫学; 肠道微生物生态失衡与代谢相关脂肪性肝病肝外并发症。5-18章为各论, 分别介绍代谢相关脂肪性肝病肝外并发症与机体各系统疾病的相关性。可为消化科、肝病科、内分泌代谢科、普外科、肿瘤科、影像科、其他相关科临床医师和从事MAFLD研究的人员学习和参考。

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