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超声内镜辅助下内镜黏膜下切除术对食管癌前病变患者肿瘤标志物及应激反应指标的影响*

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摘要 目的:探讨超声内镜(EUS)辅助下内镜黏膜下切除术(EMR)对食管癌前病变患者肿瘤标志物及应激反应指标的影响。**方法:**选择山东大学齐鲁医院青岛院区消化内科于2016年3月至2018年4月期间收治的食管癌前病变患者137例,采用随机数字表法将患者分为常规组($n=68$,常规胃镜下行EMR)和EUS组($n=69$,EUS辅助下行EMR),比较两组患者临床指标,比较两组术前、术后血清肿瘤标志物及应激反应指标水平,比较两组术前、术后1周相关遗传学分子水平。**结果:**EUS组手术时间、术后流质饮食时间均短于常规组($P<0.05$),并发食管黏膜小穿孔例数、使用钛夹止血例数均少于常规组($P<0.05$)。两组患者术后肿瘤特异性生长因子(TSGF)、细胞角蛋白19血清片段21-1(CYFRA21-1)、鳞状上皮细胞癌抗原(SCC-Ag)均较术前升高,但EUS组低于常规组($P<0.05$)。两组患者术后肾上腺素(E)、去甲肾上腺素(NE)、肾素(R)、血管紧张素II(Ang II)、醛固酮均较术前升高,但EUS组低于常规组($P<0.05$)。两组患者术后1周细胞周期素E(Cyclin E)、转化生长因子- α (TGF- α)均较术前降低,且EUS组低于常规组($P<0.05$)。**结论:**相比于常规胃镜,经EUS辅助下EMR治疗食管癌前病变可有效改善患者的临床指标,减轻患者应激反应,有利于降低血清肿瘤标志物及遗传学分子水平。

关键词:超声内镜;内镜黏膜下切除术;食管癌前病变;肿瘤标志物;应激反应

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Effect of Endoscopic Submucosal Resection Assisted by Endoscopic Ultrasonography on Tumor Markers and Stress Response Indexes in Patients with Esophageal Precancerous Lesions*

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ABSTRACT Objective: To investigate the effect of endoscopic submucosal resection (EMR) assisted by endoscopic ultrasonography (EUS) on tumor markers and stress response indexes in patients with esophageal precancerous lesions. **Methods:** A total of 137 patients with esophageal precancerous lesions, who were admitted to Gastroenterology Department of Qilu Hospital Qingdao District of Shandong University from March 2016 to April 2018, were selected. The patients were divided into routine group ($n=68$, routine gastroscopy EMR) and EUS group ($n=69$, EUS-assisted EMR). The clinical indicators, the serum tumor markers and stress response indexes before operation and after operation, and the genetic molecules levels before operation and 1 weeks after operation were compared between the two groups. **Results:** The operation time and the fluid diet time of EUS group were shorter than those of routine group ($P<0.05$), and the number of small perforation of esophageal mucosa and hemostasis with titanium clip were less than those of routine group ($P<0.05$). The levels of tumor specific growth factor (TSGF), cytokeratin 19 serum fragment 21-1 (CYFRA21-1) and squamous cell carcinoma antigen (SCC-Ag) in both groups were higher than those before operation, but the above indexes in EUS group were lower than those in routine group ($P<0.05$). Postoperative levels of epinephrine (E), norepinephrine (NE), renin (R), angiotensin II (Ang II) and aldosterone in both groups were higher than those before operation, but the above indexes in EUS group were lower than those in routine group ($P<0.05$). The cyclin E (Cyclin E) and transforming growth factor- α (TGF- α) 1 week after operation in the two groups were lower than before operation, and the above indexes in EUS group were lower than those in routine group ($P<0.05$). **Conclusion:** Compared with routine gastroscopy, EMR assisted by EUS, in the treatment of esophageal precancerous lesions, can effectively improve the clinical indicators, alleviate the stress response of patients, and reduce the level of serum tumor markers and genetic molecules.

Key words: Endoscopic ultrasonography; Endoscopic submucosal resection; Esophageal precancerous lesions; Tumor markers; Stress response

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前言

食管癌是临床常见的消化道恶性肿瘤之一,全世界每年约有 30 万人死于食管癌,我国为食管癌多发地区,每年平均病死约 15 万人^[1,2]。伴随着近年来人们对恶性肿瘤筛查的重视,早期食管癌及食管癌前病变的检出率呈较高趋势^[3,4]。食管癌前病变一经诊断,多需立即接受手术切除治疗。内镜黏膜下切除术(Endoscopic submucosal resection, EMR)因其切除率高、术后恢复快、可为患者提供更高的生活质量等优点已成为临床治疗食管癌前病变的常用术式^[5,6]。在应用 EMR 治疗时,由于病灶范围累及范围较息肉深,常规胃镜直视下对于判断病变深度尚存在一定缺陷,致使无法彻底切除病灶部位导致肿瘤残留或者过度切除引起机体更强烈的应激反应^[7,8]。超声内镜(Endoscopic ultrasonography, EUS)是新型胃镜检查手段,可清晰显示食管管壁的各层结构,提高黏膜下切除的准确性^[9,10]。本研究通过比较 EUS 辅助下与常规胃镜辅助下 EMR 对食管癌前病变患者肿瘤标志物及应激反应的影响,以期为临床治疗食管癌前病变提供参考。

1 资料和方法

1.1 临床资料

选择山东大学齐鲁医院青岛院区消化内科于 2016 年 3 月至 2018 年 4 月期间收治的食管癌前病变患者 137 例,纳入标准:(1)均符合《实用外科学》^[11]中有关食管癌前病变的相关标准;(2)均具备 EMR 手术指征;(3)患者临床资料完整;(4)患者及其家属知情本次研究并已签署了同意书。排除标准:(1)合并其他恶性肿瘤者;(2)食管存在其他病变者;(3)合并全身感染性疾病者;(4)合并内分泌系统疾病者;(5)合并血液系统疾病者;(6)伴精神疾病及认知功能障碍者。采用随机数字表法将患者分为常规组($n=68$)和 EUS 组($n=69$),其中常规组男 37 例,女 31 例,年龄 31~68 岁,平均(43.91 ± 6.32)岁;病变位置:食管上段 22 例,食管中段 28 例,食管下段 18 例;病灶大小 0.4~9 cm,平均(3.91 ± 0.45)cm;不典型增生 33 例,原位癌 35 例。EUS 组男 35 例,女 34 例,年龄 30~69 岁,平均(42.83 ± 5.18)岁;病变位置:食管上段 20 例,食管中段 27 例,食管下段 22 例;病灶大小 0.6~10 cm,平均(4.06 ± 0.52)cm;不典型增生 34 例,原位癌 35 例。两组患者一般资料比较无差异($P>0.05$),均衡可比。本研究已获得我院伦理学委员会批准进行。

1.2 方法

EUS 组患者给予 EUS 辅助下 EMR 术式,具体操作如下:行 EUS 检查,确定病灶部位及深度,EUS 直视下,于距离病灶边缘 2 mm 处的 0 点或 12 点方向将注射针头插入,注射 5 mL 肾上腺素生理盐水注射液(1:10000),插入深度以超声判断下的病灶深度为标准。肌肉层、黏膜层分离后,以圈套器套住病灶,缓慢收紧,采取高频电刀进行切割,待止血后将手术切口闭合。常规组患者给予常规胃镜辅助下 EMR 术式,操作如下:行常规消化内镜检查,确定病灶范围,内镜直视下于距离病灶边缘 2 mm 处的 0 点或 12 点方向将注射针头插入,注射 5 mL 肾上腺素生理盐水注射液(1:10000)以及病灶切除。病灶切除方式同 EUS 组。术后两组均给予常规抗感染处理。

1.3 观察指标

记录手术时间、术后流质饮食时间、并发食管黏膜小穿孔例数、使用钛夹止血例数等。于术前、术后抽取患者外周血 4 mL,用于检测血清肿瘤标志物、应激反应指标,于术前、术后 1 周抽取患者外周血 2 mL,用于检测遗传学分子,均 3000 r/min 离心 8 min,离心半径 12 cm,取上清液,置于 -40℃ 冰箱中待测。采用酶联免疫吸附法检测血清肿瘤标志物[肿瘤特异性生长因子(Tumor specific growth factor, TSGF)、细胞角蛋白 19 血清片段 21-1(Cytokeratin 19 serum fragment 21-1, CYFRA21-1)、鳞状上皮细胞癌抗原(Squamous cell carcinoma antigen, SCC-Ag)]、应激反应指标[肾上腺素(Epinephrine, E)、去甲肾上腺素(Norepinephrine, NE)、肾素(Renin, R)、血管紧张素 II(Angiotensin I-I, Ang II)、醛固酮)、遗传学分子[细胞周期素 E(Cyclin E)、转化生长因子- α (Transforming growth factor- α , TGF- α)]水平,试剂盒均购自武汉博士德生物科技有限公司,严格遵守试剂盒说明书进行操作。

1.4 统计学方法

采用 SPSS21.0 进行统计学分析,计量资料采用均数 $\pm$ 标准差($\bar{x} \pm s$)描述,两组比较采用独立样本 t 检验;计数资料采用率(%)描述,两组比较采用 χ^2 检验;以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者临床指标情况比较

EUS 组手术时间、术后流质饮食时间均短于常规组($P<0.05$),并发食管黏膜小穿孔例数、使用钛夹止血例数均少于常规组($P<0.05$),详见表 1。

表 1 两组患者临床指标情况比较

Table 1 Comparison of clinical indicators between two groups of patients

Groups	Operation time(min)	Postoperative fluid diet time (d)	Number of small perforation of esophageal mucosa [n(%)]	Number of hemostasis with titanium clip [n(%)]
Routine group($n=68$)	41.22 $\pm$ 3.03	1.95 $\pm$ 0.37	8(11.76)	10(14.71)
EUS group($n=69$)	28.37 $\pm$ 4.15	1.23 $\pm$ 0.24	1(1.45)	3(4.35)
t/χ^2	20.674	13.532	5.937	4.278
P	0.000	0.000	0.015	0.039

2.2 两组患者肿瘤标志物水平比较

两组患者术前 TSGF、CYFRA21-1、SCC-Ag 水平比较差异无统计学意义($P>0.05$),两组患者术后 TSGF、CYFRA21-1、

SCC-Ag 水平均较术前升高,但 EUS 组低于常规组($P<0.05$),详见表 2。

表 2 两组患者肿瘤标志物水平比较($\bar{x} \pm s$)Table 2 Comparison of tumor markers between two groups of patients($\bar{x} \pm s$)

Groups	TSGF(U/mL)		CYFRA21-1(ng/mL)		SCC-Ag(ng/mL)	
	Before operation	After operation	Before operation	After operation	Before operation	After operation
Routine group(n=68)	31.04± 7.98	139.12± 15.76*	3.18± 0.56	12.35± 1.24*	1.34± 0.91	2.94± 0.53*
EUS group(n=69)	30.91± 8.24	76.43± 10.62*	3.21± 0.51	6.27± 0.93*	1.41± 1.02	2.17± 0.62*
t	0.094	27.339	0.328	32.498	0.424	7.808
P	0.925	0.000	0.743	0.000	0.672	0.000

Note: compared with before operation, * $P<0.05$.

2.3 两组患者应激反应指标水平比较

计学意义($P>0.05$),两组患者术后 E、NE、R、Ang II、醛固酮水

两组患者术前 E、NE、R、Ang II、醛固酮水平比较差异无统

平均较术前升高,但 EUS 组低于常规组($P<0.05$),详见表 3。表 3 两组患者应激反应指标水平比较($\bar{x} \pm s$)Table 3 Comparison of stress response indexes between two groups of patients($\bar{x} \pm s$)

Groups	E(ng/mL)		NE(ng/mL)		R(ng/mL)		Ang II(ng/mL)		Aldosterone(ng/mL)	
	Before operation	After operation	Before operation	After operation	Before operation	After operation	Before operation	After operation	Before operation	After operation
Routine group(n=68)	29.64± 5.27	114.57± 15.89*	42.38± 7.13	170.23± 16.12*	0.26± 0.05	1.89± 0.25*	14.52± 4.18	56.13± 5.63*	36.44± 7.32	122.24± 14.38*
EUS group(n=69)	30.53± 6.25	69.74± 14.47*	41.35± 5.17	95.97± 12.67*	0.25± 0.03	1.21± 0.13*	13.93± 5.22	29.78± 6.14*	35.46± 6.24	68.52± 8.43*
t	0.900	17.270	0.969	30.002	1.422	20.015	0.730	26.170	0.844	26.721
P	0.369	0.000	0.334	0.000	0.157	0.000	0.467	0.000	0.400	0.000

Note: compared with before operation, * $P<0.05$.

2.4 两组患者相关遗传学分子水平比较

义($P>0.05$),两组患者术后 1 周 Cyclin E、TGF- α 水平均较术前两组患者术前 Cyclin E、TGF- α 水平比较差异无统计学意降低,且 EUS 组低于常规组($P<0.05$),详见表 4。表 4 两组患者相关遗传学分子比较($\bar{x} \pm s$)Table 4 Comparison of relevant genetic molecules between two groups of patients($\bar{x} \pm s$)

Groups	Cyclin E(ng/mL)		TGF- α (ng/mL)	
	Before operation	1 week after operation	Before operation	1 week after operation
Routine group(n=68)	49.68± 5.21	38.67± 6.08*	106.24± 12.57	78.17± 8.14*
EUS group(n=69)	50.15± 6.76	29.65± 5.58*	107.13± 10.41	43.52± 6.55*
t	0.455	9.049	0.452	27.469
P	0.650	0.000	0.652	0.000

Note: compared with before operation, * $P<0.05$.

3 讨论

食管癌的主要发病过程为正常黏膜 - 炎症 - 单纯增生 - 非典型增生癌 - 原位癌 - 浸润癌,而食管癌前病变则属于非典型增生癌 - 原位癌这一过程,在疾病处于食管癌前病变阶段时,给予手术切除可有效阻断疾病进展,改善患者远期预后^[12-14]。EMR 是目前临床治疗癌前病变、消化道息肉的常用方式,通过结合电凝切除治疗以及黏膜注射治疗等优点,有效分离病灶组织,同时还可收缩血管减少术中出血量^[15-17]。目前 EMR 治疗消化道息肉的疗效已得到证实^[18],而有关其应用于食管癌前病变的治疗尚需要大样本试验证实。由于食管癌前病灶特征与息肉

尚有一定差距,息肉病灶深度略浅,易于黏膜下注射,而食管癌前病灶深浅不一,黏膜下注射难度较大,过浅不利于病灶分离,过深则增加切除范围,加重机体损伤,同时也易引起消化道穿孔等并发症发生风险^[19,20]。EUS 作为近年来新兴的诊疗技术,可清晰显示食管管壁结构,确保进行 EMR 能够准确辨认病灶组织与正常组织,利于手术的顺利进行^[21,22]。

本次研究结果显示,EUS 组手术时间、术后流质饮食时间较短、并发食管黏膜小穿孔例数、使用钛夹止血例数较少,表明 EUS 辅助下行 EMR,操作简单、迅速,对消化道局部损伤较小,这与郑建臣等人^[23]的研究结果基本一致。这源于超声内镜自身的优势:准确判断切除范围以及黏膜下注射深度,可最大程度

的保护患者正常组织。由于内镜的持续置入为强烈应激源,加之术中切除组织容易引发患者激烈的应激反应,应激反应激活后,交感神经活性增强,E、NE、R 合成分泌增加,引起患者血流动力学波动,同时 R 可刺激 Ang II、醛固酮的分泌,影响水钠平衡^[24,25]。本研究中两组患者术后应激反应指标均较术前升高,但 EUS 组低于常规组,表明相较于常规胃镜,EUS 辅助下行 EMR 可进一步减轻患者应激反应,这主要是 EUS 可避免过度切除正常组织,术后应激反应激活程度较轻^[26]。本研究结果表明两组患者术后血清肿瘤标志物均较术前升高,但 EUS 组低于常规组,表明 EUS 下行手术切除,有利于降低血清肿瘤标志物水平,肿瘤标志物作为肿瘤灶合成的具有生物活性的分子,分泌后进入血液,可反映肿瘤的负荷程度^[27]。这主要是 EUS 操作精准度高,可减少对病灶组织的牵拉作用,有利于保护组织,减少组织内的肿瘤标志物释放。由于病情处于食管癌前病变时,相关遗传学分子已发生改变,包括 Cyclin E、TGF- α 等分子表达量不断升高,进而造成细胞增殖能力增强,最终发展成为恶性肿瘤^[28,29]。本次研究中两组患者术后 1 周 Cyclin E、TGF- α 均较术前降低,且 EUS 组低于常规组。再一次证实 EUS 辅助下 EMR 治疗食管癌前病变,有利于降低遗传学分子水平,这主要是由于 EUS 下手术切除对食管局部组织创伤较小,遗传学分子进入血液中的量相对较少^[30]。本研究的不足之处在于未对患者远期预后进行考察,后续报道将扩大样本量,增加随访时间以获取更为准确的数据。

综上所述,相比于常规胃镜,经 EUS 辅助下 EMR 治疗食管癌前病变,优势明显,可有效改善患者临床指标,血清肿瘤标志物及遗传学分子水平均得到有效控制,同时还可以减轻患者应激反应,临床应用价值较高。

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