论著·临床研究

食管鳞癌内镜黏膜下剥离术后T1b患者再治疗策略分析

朱开元*，苏瑜琛*，刘智超，章　宏，李春光，张　杰，李志刚
上海市胸科医院/上海交通大学医学院附属胸科医院胸外科，上海 200030

［摘要］**目的**·比较食管癌根治性切除术、同步放射和化学治疗与单纯随访观察3种策略对经内镜黏膜下剥离术（endoscopic submucosal dissection，ESD）治疗后T1b浅表食管鳞癌患者预后的影响。**方法**·回顾性分析2016年5月—2021年5月于上海市胸科医院治疗的经ESD术后病理证实为pT1b期的67例食管鳞癌患者的临床资料。根据ESD术后追加的治疗方式分为追加手术组（S组）、放化疗组（CRT组）和观察组（O组）。采用χ^2检验比较3组患者的临床基线资料和病理信息。采用Kaplan-Meier生存曲线和log-rank检验比较3组患者的无病生存期（disease free survival，DFS）和无复发生存期（recurrence free survival，RFS），并采用Cox比例风险回归模型对DFS和RFS进行单因素及多因素分析。**结果**·67例患者中，S组23例，CRT组19例，O组25例。3组组间年龄（*P*=0.080）、性别（*P*=0.078）、肿瘤大小（*P*=0.485）、食管癌临床分段（*P*=0.655）、环周累及（*P*=0.310）、分化程度（*P*=0.084）、浸润深度（*P*=0.066）、淋巴脉管侵犯（*P*=0.279）比较，差异均无统计学意义。经（42.6±16.7）个月的随访，共10例（14.9%）患者复发，其中6例（60%）为局部复发，2例（20%）为区域淋巴结转移，2例（20%）为远处转移；S组、CRT组、O组的中位复发时间分别为40.1、36.6、22.1个月，3年DFS分别为100%、89.5%和74.5%（*P*-trend=0.040）。多因素Cox分析显示，追加手术是改善RFS的独立保护性因素（*HR*=0.097，95%*CI* 0.010~0.956，*P*=0.046）。**结论**·对于浅表食管鳞癌ESD后证实为pT1b期的患者，追加手术可以显著减少远期复发可能。

［关键词］浅表食管癌；食管鳞状细胞癌；病理分期：内镜黏膜下剥离术；追加治疗
［DOI］10.3969/j.issn.1674-8115.2024.01.013　［中图分类号］R735.1　［文献标志码］A

Adjuvant strategies for patients with T1b invasion after endoscopic submucosal dissection for esophageal squamous cell carcinoma

ZHU Kaiyuan*, SU Yuchen*, LIU Zhichao, ZHANG Hong, LI Chunguang, ZHANG Jie, LI Zhigang
Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China

[Abstract] **Objective**·To compare the prognostic effects of radical resection of esophageal cancer, concurrent chemoradiotherapy and simple follow-up observation on the prognosis of patients with T1b invasion of superficial esophageal squamous cell carcinoma after endoscopic submucosal dissection (ESD). **Methods**·From May 2016 to May 2021, the clinical data of 67 patients with esophageal squamous cell carcinoma who were pathologically confirmed as pT1b after ESD and treated in Shanghai Chest Hospital were retrospectively analyzed. According to the additional treatment after ESD, the patients were divided into additional surgery group (S group), chemoradio-therapy group (CRT group) and observation group (O group). χ^2 test was used to compare the clinical baseline data and pathological information of the three groups of patients. The Kaplan-Meier survival curve and log-rank test were used to compare the disease free survival (DFS) and recurrence free survival (RFS) of the three groups of patients, and the Cox proportional hazards regression model was used on DFS and RFS by univariate and multivariate analysis. **Results**·Among all 67 patients, there were 23 cases in the S group, 19 cases in the CRT group, and 25 cases in the O group. There was no significant difference in age (*P*=0.080), gender (*P*=0.078), tumor length (*P*=0.485), tumor location (*P*=0.655), lesion circumferential ratio (*P*=0.310), histological grading (*P*=0.084), depth of tumor invasion (*P*=0.066) and lymphovascular invasion (*P*=0.279) among the three groups. During (42.6±16.7) months of follow-up, tumor recurrence was observed in 10 cases (14.9%), including 6 patients (60%) with local recurrence, 2 patients (20%) with regional lymph recurrence and 2 patients (20%) with distant metastasis. The median recurrence time of group S, group CRT, and group O was 40.1, 36.6, and 22.1 months, and the 3-year DFSs were 100%, 89.5%, and 74.5% (*P*-trend=0.040). Multivariate Cox analysis showed that additional esophagectomy was the key to improving independent

[基金项目] 上海交通大学医学院“双百人”项目（20181816）。
[作者简介] 朱开元（1999—），男，满族，博士生；电子信箱：zhukaiyuan112@163.com。苏瑜琛（1983—），男，主治医师，硕士；电子信箱：inalcohol@126.com。*为共同第一作者。
[通信作者] 李志刚，电子信箱：zhigang.li@shsmu.edu.cn。
[Funding Information] "Two-hundred Talents" Program of Shanghai Jiao Tong University School of Medicine (20181816).
[Corresponding Author] LI Zhigang, E-mail: zhigang.li@shsmu.edu.cn.

protective factors of RFS (*HR*=0.097, 95%*CI* 0.010 – 0.956, *P*=0.046). **Conclusion**·For patients with superficial esophageal squamous cell carcinoma confirmed as pT1b after ESD, additional surgery can significantly reduce the possibility of long-term recurrence.

[Key words] superficial esophageal cancer; esophageal squamous cell carcinoma; pathology stage; endoscopic submucosal dissection; additional treatment

食管癌是全球范围内常见的恶性肿瘤之一，发病率和病死率在全部癌症类型中分别排在第七位和第六位[1]。近年来，随着食管癌早诊早治策略的贯彻和高危人群早期筛查意识的提高，浅表食管癌被检出的概率逐步提升[2]。内镜黏膜下剥离术（endoscopic submucosal dissection，ESD）已逐渐被推荐用于浅表食管鳞癌（cT1N0M0）的初始治疗。当行ESD后患者病理诊断结果为病变累及黏膜下层（T1b）时，通常推荐追加治疗以预防局部和区域淋巴结转移[3-9]，但最佳治疗策略尚未达成一致[5,9-10]。

目前，对于经ESD治疗后的肿瘤已经侵犯到黏膜下层（pT1b）的食管鳞癌患者的治疗策略主要有3类：最常见的传统策略是采用根治性手术切除，可以有效地清扫潜在的转移淋巴结，达到根治性切除的目的，但患者需要承受手术带来的创伤以及术后并发症的风险。另一种选择是追加同步放射治疗和化学治疗（简称放化疗），这种方案具有独特的保器官优势，多项研究也证实了其安全性与有效性[11-13]。然而，目前尚无有力的证据判断二者预后的优劣。此外，有些患者存在较高的手术风险或不愿意接受放化疗。研究显示对于大于75岁的老年患者群体，追加手术并未带来生存上的获益，单纯随访也是一种选择[14]。

本研究拟通过回顾性分析单中心浅表食管鳞癌经ESD后证实为pT1b的患者资料，探讨手术、放化疗以及单纯随访作为3种不同补救性策略对预后的影响，为此类患者未来临床治疗选择提供参考。

1　对象与方法

1.1　研究对象

回顾性分析2016年5月—2021年5月于上海市胸科医院就诊的经ESD术后病理证实为pT1b期食管癌患者71例，其中包含“一项比较外科切除与放化疗治疗ESD术后cN0-pT1b期食管鳞癌患者的前瞻性多中心随机对照Ⅲ期临床试验（Ad-ESD研究）”（ClinicalTrials.gov注册编号：NCT04135664）中入组患者13例。纳入标准：年龄为18~80岁；无淋巴结及远处转移；行ESD前未接受过食管癌相关治疗；病理类型为鳞状细胞癌；ESD术后病理证实肿瘤浸润至黏膜下层。排除标准：肿瘤位于颈部食管或胃食管交接部；病理类型包含非鳞癌成分；失访。

最终纳入67例pT1b期患者，并根据追加的治疗方案进行分组。追加根治性手术切除者，分入追加手术组（S组，23例）；追加同步放化疗者，分入放化疗组（CRT组，19例）；仅单纯随访的患者，分入观察组（O组，25例）。

1.2　研究方法

1.2.1　临床资料　肿瘤病理分期参照第8版美国癌症联合委员会（American Joint Committee on Cancer，AJCC）食管癌TNM分期标准[15]。病理组织学分类参照2019版WHO消化系统肿瘤分类标准[16]。食管癌临床分段、水平切缘状态、垂直切缘状态、淋巴脉管侵犯状态评估参照我国《食管癌诊疗指南（2022年版）》[10]。根据日本食管学会（Japanese Esophagus Society，JES）指南，pT1b-SM1定义为肿瘤浸润黏膜下层≤200 μm，pT1b-SM2定义为肿瘤浸润黏膜下层>200 μm[5,9]。

1.2.2　再治疗方法　追加食管癌根治术及同步放化疗的治疗操作均依据我国《食管癌诊疗指南（2022年版）》[10]。食管癌根治术类型包括行至少二野淋巴结清扫的传统开放式、腔镜辅助或机器人辅助下的McKeown食管癌切除术、Ivor Lewis食管癌切除术。同步放化疗中化疗药物方案包括紫杉醇+铂类或顺铂+5-氟尿嘧啶方案，放疗处方剂量为60 Gy，可按患者实际情况降低放疗剂量至50.4 Gy。

1.2.3　术后随访　术后通过门诊复查评估或电话等方式对患者进行随访。随访内容包括上消化道内镜、CT以及肿瘤标志物检测，并在必要时采用超声、正电子发射计算机断层显像（positron emission tomography-computed tomography，PET-CT）、骨扫描、磁共振成像等检查评估。患者ESD术后1年内应

在第1个月、第3个月、第6个月、第12个月各随访1次，此后至少每半年随访1次，随访截止日期为2023年5月1日。

1.3 统计学分析

采用SPSS 26.0统计软件对临床资料进行统计学分析。分类变量以n（%）表示，采用Pearson χ^2检验、连续校正检验或Fisher精确概率法进行比较。连续变量以$\bar{x}\pm s$表示，采用Welch检验或多独立样本Kruskal-Wallis检验进行比较。生存变量采用Kaplan-Meier法计算，绘制生存曲线后，采用log-rank检验对患者的无病生存期（disease free survival，DFS）和无复发生存期（recurrence free survival，RFS）进行比较。应用Cox回归模型进行单因素和多因素回归，分析肿瘤复发危险因素。P<0.05表示差异具有统计学意义。

2 结果

2.1 基线资料

3组患者的基线临床资料，包括年龄、性别、烟酒史、肿瘤大小、食管癌临床分段、环周累及范围、分化程度、浸润深度、垂直切缘情况、水平切缘情况以及淋巴脉管侵犯情况比较，差异均无统计学意义，资料具有可比性（表1）。

表1 3组患者基线特征比较

Tab 1 Comparison of baseline characteristics among the 3 groups of patients

Characteristic	Total (n=67)	S group (n=23)	CRT group (n=19)	O group (n=25)	P value
Age/years	65.3±7.4	63.1±4.9	64.4±5.5	68.1±9.5	0.080
Gender/n(%)					0.078
Male	54 (80.6)	22 (95.7)	14 (73.7)	18 (72.0)	
Female	13 (19.4)	1 (4.3)	5 (26.3)	7 (28.0)	
Smoking history/n(%)					0.213
None	22 (32.8)	5 (21.7)	6 (31.6)	11 (44.0)	
Yes	39 (58.2)	17 (73.9)	10 (52.6)	12 (48.0)	
Unknown①	6 (9.0)	1 (4.3)	3 (15.8)	2 (8.0)	
Alcohol history/n(%)					0.834
None	28 (41.8)	9 (39.1)	8 (42.1)	11 (44.0)	
Yes	33 (49.2)	13 (56.5)	8 (42.1)	12 (48.0)	
Unknown①	6 (9.0)	1 (4.3)	3 (15.8)	2 (8.0)	
Tumor length/cm	3.7±2.1	4.2±2.6	3.1±1.1	3.7±2.1	0.485
Tumor location/n(%)					0.655
Upper	6 (9.0)	2 (8.7)	3 (15.8)	1 (4.0)	
Middle	26 (38.8)	9 (39.1)	8 (42.1)	9 (36.0)	
Lower	35 (52.2)	12 (52.2)	8 (42.1)	15 (60.0)	
Lesion circumferential ratio/n(%)					0.310
<0.50	20 (29.9)	5 (21.7)	8 (42.1)	7 (28.0)	
≥0.50 and<0.75	31 (46.3)	13 (56.5)	9 (47.4)	9 (36.0)	
≥0.75	12 (17.9)	5 (21.7)	1 (5.3)	6 (24.0)	
Unknown①	4 (6.0)	0 (0)	1 (5.3)	3 (12.0)	
Histological grading/n(%)					0.084
G1	14 (20.9)	5 (21.7)	4 (21.1)	5 (20.0)	
G2	29 (43.3)	5 (21.7)	9 (47.4)	15 (60.0)	
G3	14 (20.9)	9 (39.1)	2 (10.5)	3 (12.0)	
Gx	10 (14.9)	4 (17.4)	4 (21.1)	2 (8.0)	
Pathology T stage after ESD/n(%)					0.066
pT1b-SM1	28 (41.8)	7 (30.4)	6 (31.6)	15 (60.0)	
pT1b-SM2	39 (58.2)	16 (69.6)	13 (68.4)	10 (40.0)	

Continued Tab

Characteristic	Total (*n*=67)	S group (*n*=23)	CRT group (*n*=19)	O group (*n*=25)	*P* value
Vertical margin/*n*(%)					0.075
Positive	18 (26.9)	9 (39.1)	6 (31.6)	3 (12)	
Negative	48 (71.6)	13 (56.5)	13 (68.4)	22 (88)	
Unknown①	1 (1.5)	1 (4.3)	0 (0)	0 (0)	
Horizontal margin/*n*(%)					0.814
Positive	21 (31.3)	6 (26.1)	6 (31.6)	9 (36.0)	
Negative	45 (67.2)	16 (69.6)	13 (68.4)	16 (64.0)	
Unknown①	1 (1.5)	1 (4.3)	0 (0)	0 (0)	
Lymphovascular invasion/*n*(%)					0.279
Positive	7 (10.4)	4 (17.4)	2 (10.5)	1 (4.0)	
Negative	57 (85.1)	17 (73.9)	17 (89.5)	23 (92.0)	
Unknown①	3 (4.5)	2 (8.7)	0 (0)	1 (4.0)	

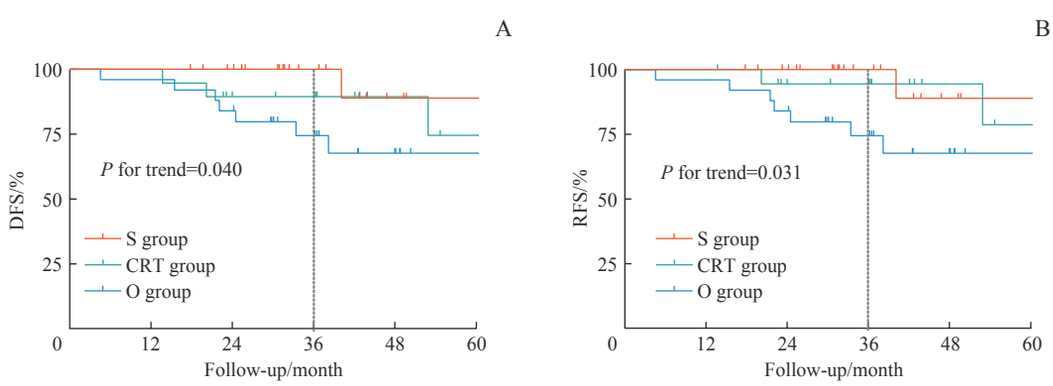
Note: ①Missed data of clinical records.

2.2　复发情况

全体患者随访时间为（42.6±16.7）个月。其中，S组为（40.0±17.2）个月，CRT组为（42.1±17.3）个月，O组为（45.3±16.1）个月，3组随访时间具有可比性（*P*=0.524）。随访期间共有10例（14.9%）患者复发，其中S组1例（4.3%），CRT组2例（10.5%），O组7例（28.0%）。复发患者中6例（60%）为局部复发，2例（20%）为区域淋巴结转移，2例（20%）为远处转移。S组、CRT组以及O组的中位复发时间分别为40.1、36.6、22.1个月。

2.3　生存结果

随访期间共有3例患者死亡，S组、CRT组以及O组各1例。CRT组死亡患者死亡原因为非肿瘤死亡（脑梗死），其余2例患者均因肿瘤复发后再治疗无效死亡。S组、CRT组和O组的3年DFS比例分别为100%、89.5%和74.5%（趋势性检验*P*-trend=0.040），3组的3年RFS比例分别为100%、94.4%和74.5%（趋势性检验*P*-trend=0.031）。采用log-rank检验分别比较2组间的DFS和RFS生存曲线，结果显示S组的DFS和RFS均优于O组（均*P*=0.048，*HR*均为0.039~0.636）；S组与CRT组的DFS和RFS比较，差异均无统计学意义（*P*=0.350，*P*=0.661）；CRT组与O组的DFS和RFS比较，差异也无统计学意义（*P*=0.318，*P*=0.152）。详见图1。



Note: A. DFS curve. B. RFS curve.

图1　3组间DFS和RFS的生存曲线比较

Fig 1　Kplan-Meier curves for DFS and RFS

2.4　单因素及多因素分析

将通过单因素分析筛选出的*P*<0.1的影响因素与浸润深度、分化程度和淋巴脉管侵犯3个经典预后不良危险因素纳入Cox比例风险回归模型进行多因素分析，结果显示追加手术（*HR*=0.097，95%*CI* 0.010~0.956，*P*=0.046）是改善RFS的独立保护性因素（表2、3）。

表2 DFS和RFS危险因素的单因素分析

Tab 2 Univariate analysis of risk factors for DFS and RFS

Characteristic	DFS		RFS	
	HR (95%*CI*)	*P* value	*HR* (95%*CI*)	*P* value
Gender (male *vs* female)	1.160 (0.250–5.377)	0.850	1.035 (0.219–4.886)	0.965
Age (<65 years *vs* ≥65 years)	0.473 (0.138–1.620)	0.223	0.559 (0.157–1.985)	0.368
Smoke (yes *vs* none)	1.507 (0.397–5.723)	0.547	1.313 (0.337–5.125)	0.695
Alcohol (yes *vs* none)	2.274 (0.599–8.626)	0.227	1.981 (0.508–7.723)	0.325
Tumor length (<2 cm *vs* ≥2 cm)	1.722 (0.524–5.661)	0.371	1.364 (0.384–4.852)	0.631
Tumor location				
Upper	Reference=1		Reference=1	
Middle	1.464 (0.170–12.617)	0.729	1.497 (0.174–12.908)	0.714
Lower	1.080 (0.126–9.288)	0.944	0.880 (0.098–7.912)	0.909
Lesion circumferential ratio				
<0.50	Reference=1		Reference=1	
≥0.50 and<0.75	0.852 (0.190–3.816)	0.835	1.279 (0.234–6.997)	0.777
≥0.75	1.116 (0.186–6.702)	0.905	1.678 (0.235–11.965)	0.605
Histological grading (G1/G2 *vs* G3/Gx)	0.544 (0.164–1.800)	0.318	0.441 (0.126–1.540)	0.199
Pathology T stage (SM1 *vs* SM2)	0.394 (0.083–1.862)	0.240	0.449 (0.093–2.171)	0.319
Vertical margin (positive *vs* negative)	2.027 (0.615–6.680)	0.245	1.606 (0.450–5.731)	0.465
Horizontal margin (positive *vs* negative)	3.379 (0.980–11.651)	0.054	2.843 (0.794–10.186)	0.108
Lymphovascular invasion (positive *vs* negative)	1.697 (0.359–8.017)	0.504	0.524 (0.109–2.532)	0.421
Treatment				
Surgery	Reference=1		Reference=1	
CRT	3.204 (0.331–31.029)	0.315	2.092 (0.188–23.284)	0.548
Observation	6.403 (0.788–52.061)	0.082	6.375 (0.784–51.833)	0.083

表3 DFS和RFS危险因素的多因素分析

Tab 3 Multivariate analysis of risk factors for DFS and RFS

Characteristic	DFS		RFS	
	HR (95%*CI*)	*P* value	*HR* (95%*CI*)	*P* value
Horizontal margin				
Positive	2.646 (0.623–11.228)	0.245	1.970 (0.413–9.388)	0.395
Negative	Reference=1		Reference=1	
Treatment				
Surgery	0.109 (0.011–1.055)	0.056	0.097 (0.010–0.956)	0.046
CRT	0.330 (0.066–1.658)	0.178	0.201 (0.031–1.316)	0.094
Observation	Reference=1		Reference=1	
Pathology T stage				
SM1	Reference=1		Reference=1	
SM2	2.833 (0.473–16.961)	0.254	2.537 (0.396–16.261)	0.326
Histological grading				
G1/G2	Reference=1		Reference=1	
G3/Gx	2.569 (0.601–10.980)	0.203	3.315 (0.678–16.214)	0.139
Lymphovascular invasion				
Positive	0.895 (0.140–5.727)	0.906	2.537 (0.396–16.261)	0.913
Negative	Reference=1		Reference=1	

3　讨论

内镜下切除已经逐渐成为局限性黏膜内食管鳞癌的标准初始治疗推荐方法。但由于目前评估手段对于肿瘤浸润黏膜下层的患者，判断的准确度不高，仍会在临床中遇到ESD后病理确诊是T1b黏膜下侵犯的情况[17-19]。对于病理提示pT1b的患者，目前没有最佳治疗方案的共识。在本项单中心回顾性研究中，我们比较了追加外科手术、追加放化疗以及单纯随访3种策略对于经ESD治疗后为pT1b的浅表食管鳞癌患者的预后。结果显示S组、CRT组和O组的3年DFS和RFS依次下降；并且，S组的生存率显著优于O组，而S组与CRT组的生存率没有显著差异。本研究结果提示：经ESD治疗后的pT1b浅表食管鳞癌患者，追加外科手术治疗可以有效预防远期复发，追加放化疗也可以作为替代方案，供想要保器官的患者选择。

追加外科手术是行ESD后证实为pT1b患者的标准策略，通过对潜在的转移淋巴结进行有效的清扫，可以有效预防局部复发，获得令人满意的生存结果[4,20-22]。本研究中S组的RFS显著优于O组，证实追加外科手术治疗为经ESD治疗的pT1b食管鳞癌患者带来了生存获益。然而，追加外科手术的患者在术后难以避免会发生吻合口瘘、喉返神经损伤、肺炎等并发症，并且在一段时间内都要承受食管切除术后随饮食及消化性状改变而带来的生活质量的下降[23]。因此，部分患者会选择可以保存器官的追加放化疗作为治疗策略[24]。日本的一项针对Ⅰ期食管癌（cT1N0M0）的临床试验（JCOG9708）证实了对于没有内镜切除指证的早期食管鳞癌患者，同步放化疗具有高达87.5%的临床缓解率、80.5%的4年生存率、68%的无复发生存率以及小于10%的三级及以上不良反应发生率，确定了同步放化疗可以作为一种标准的治疗早期食管鳞癌的方法[11]。MINASHI等[25]的研究显示，对于pT1a有病理高危因素和pT1b的食管鳞癌患者，行ESD后追加放化疗的3年生存率可以达到90.7%，为行ESD后追加放化疗提供了重要的理论依据。日本临床肿瘤学会（Japan Clinical Oncology Group，JCOG）开展的JCOG0508试验[26]将浅表食管鳞癌按照黏膜切除的病理结果进行分层，并根据其病理危险程度分为观察组、预防性CRT组和根治性CRT组。结果显示：全体患者5年无复发生存率为87.5%，5年生存率为90.9%；预防性CRT组患者5年无复发生存率为86.2%，5年生存率为89.7%，治疗效果较好[27]。同时，诊断性的黏膜切除也可以改善根治性放化疗对c/pT1bN0M0期食管鳞癌患者的预后[28]。总而言之，追加放化疗可以为患者保留食管，减少患者创伤，提高患者生活质量，并获得不劣于追加外科手术患者的生存预后，作为可选的追加治疗策略具有其独特的优势。

NAKAJO等[14]的研究结果显示，对于年龄超过75岁，尤其是查尔森合并症指数（Charlson Comorbidity Index，CCI）≥2的老年人群体，在追加手术治疗时并未带来生存获益；并以此为基础提出了单纯随访作为治疗策略的可能。但该研究仅纳入了年龄超过75岁的患者，具有一定局限性。SONG等[29]的研究回顾性分析了52例非治愈性ESD后追加手术或者单纯随访患者的预后差异，结果显示2组间肿瘤特异性生存率相近。但该研究与本研究目标人群不完全相同。本研究纳入了25例拒绝接受追加治疗的患者，这部分患者在随访期间有7例（28.0%）出现了复发或转移，高于S组（4.3%）和CRT组（10.5%）；O组中位复发时间为22.1个月，也短于S组（40.1个月）和CRT组（36.6个月）；O组的DFS和RFS也均显著劣于S组（均P=0.048）。因此，对于评估后可进行外科手术的pT1b期患者，在ESD术后应追加手术治疗以获得更佳的生存期。

值得注意的是，尽管多项研究表明追加放化疗和追加手术的c/pT1bN0M0患者长期生存结果接近，但CRT组的复发率始终高于S组[12,30-31]。在JCOG0502研究[12,32-33]中，对于cT1bN0M0的食管鳞癌患者，食管癌根治术后发现高达27%的患者存在病理淋巴结阳性，手术组和放化疗组的5年RFS比例分别为81.7%（95% *CI* 75.7~86.3）和71.6%（95%*CI* 63.9~78.0），5年总生存率（overall survival，OS）分别为86.5%（95%*CI* 81.0~90.5）和85.5%（95%*CI* 78.9~90.1）。该研究认为虽然放化疗组的5年RFS比例低于手术组，但是5年OS没有显著差异，可归因于复发患者再治疗效果良好。此外，这也提示临床医师，对于T1b期食管鳞癌患者，需要采用CT、超声内镜及淋巴结穿刺等更加严谨的手段评估淋巴结状态，以期患者获得更佳的预后[34]。本研究的Cox多因素分析显示，对于pT1bN0M0期食管鳞癌患者，治疗方式的选择是影响预后的独立危险因素，这与NAITO等[31]的研究结果一致。

本研究为单中心的回顾性研究，由于研究限定在经过ESD病理证实为pT1b期的食管浅表鳞癌（cT1N0M0），此部分患者样本量较小，可能会导致统计学偏倚。另外，本研究中未涉及追加手术的患者和追加放化疗的患者治疗后并发症和生活质量的分析，未来将在进一步的前瞻性研究中进行分析与研究[35]。

综上所述，对于浅表食管鳞癌ESD后证实为pT1b的患者，追加手术可以显著降低远期复发可能。对于无法耐受手术或希望保留器官而拒绝手术的患者，可以选择追加放化疗作为治疗策略。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

伦理审批和知情同意/Ethics Approval and Patients Consent

本研究获得上海交通大学医学院附属胸科医院伦理委员会批准（伦理审批号：KS1917）。所有试验过程均遵照《赫尔辛基宣言》的伦理条例进行。受试者或其亲属已经签署知情同意书。

All experimental protocols in this study were reviewed and approved by the Ethics Committee of Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine (Approval Letter NO. KS1917), and all experimental protocols were carried out by following the guidelines of *Declaration of Helsinki*. Consent letters have been signed by the research participates or their relatives.

作者贡献/Authors′Contributions

朱开元、李志刚参与了实验设计；朱开元、苏瑜琛、章宏、李春光、张杰参与了数据收集和随访；朱开元负责数据分析；朱开元、苏瑜琛、刘智超、李志刚参与了论文的写作和修改。所有作者均阅读并同意了最终稿件的提交。

The study was designed by ZHU Kaiyuan and LI Zhigang. Clinical and survival data was collected by ZHU Kaiyuan, SU Yuchen, ZHANG Hong, LI Chunguang and ZHANG Jie. Data was analyzed by ZHU Kaiyuan. The manuscript was drafted and revised by ZHU Kaiyuan, SU Yuchen, LIU Zhichao and LI Zhigang. All the authors have read the last version of paper and consented for submission.

· Received: 2023-09-04
· Accepted: 2024-01-02
· Published online: 2024-01-28

参·考·文·献

[1] SUNG H, FERLAY J, SIEGEL R L, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2021, 71(3): 209-249.

[2] SEMENKOVICH T R, HUDSON J L, SUBRAMANIAN M, et al. Trends in treatment of T1N0 esophageal cancer[J]. Ann Surg, 2019, 270(3): 434-443.

[3] TACHIMORI Y, OZAWA S, NUMASAKI H, et al. Comprehensive registry of esophageal cancer in Japan, 2009[J]. Esophagus, 2016, 13(2): 110-137.

[4] IGAKI H, KATO H, TACHIMORI Y, et al. Clinicopathologic characteristics and survival of patients with clinical Stage I squamous cell carcinomas of the thoracic esophagus treated with three-field lymph node dissection[J]. Eur J Cardiothorac Surg, 2001, 20(6): 1089-1094.

[5] KITAGAWA Y, ISHIHARA R, ISHIKAWA H, et al. Esophageal cancer practice guidelines 2022 edited by the Japan esophageal society: part 1[J]. Esophagus, 2023, 20(3): 343-372.

[6] TAJIMA Y, NAKANISHI Y, TACHIMORI Y, et al. Significance of involvement by squamous cell carcinoma of the ducts of esophageal submucosal glands. Analysis of 201 surgically resected superficial squamous cell carcinomas[J]. Cancer, 2000, 89(2): 248-254.

[7] BOLLSCHWEILER E, BALDUS S E, SCHRÖDER W, et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas[J]. Endoscopy, 2006, 38(2): 149-156

[8] NEWTON A D, PREDINA J D, XIA L L, et al. Surgical management of early-stage esophageal adenocarcinoma based on lymph node metastasis risk[J]. Ann Surg Oncol, 2018, 25(1): 318-325.

[9] KITAGAWA Y, ISHIHARA R, ISHIKAWA H, et al. Esophageal cancer practice guidelines 2022 edited by the Japan Esophageal Society: part 2[J]. Esophagus, 2023, 20(3): 373-389.

[10] 中华人民共和国国家卫生健康委员会医政医管局. 食管癌诊疗指南(2022年版)[J]. 中华消化外科杂志, 2022, 21(10): 1247-1268.
Bureau of Medical Administration, National Health Commission of the People′s Republic of China. Standardization for diagnosis and treatment of esophageal cancer (2022 edition)[J]. Chinese Journal of Digestive Surgery, 2022, 21(10): 1247-1268.

[11] KATO H, SATO A, FUKUDA H, et al. A phase Ⅱ trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan clinical oncology group study (JCOG9708) [J]. Jpn J Clin Oncol, 2009, 39(10): 638-643.

[12] KATO K, ITO Y, NOZAKI I, et al. Parallel-group controlled trial of surgery versus chemoradiotherapy in patients with stage I esophageal squamous cell carcinoma[J]. Gastroenterology, 2021, 161(6): 1878-1886.e2.

[13] FAN X, WANG J, XIA L, et al. Efficacy of endoscopic therapy for T1b esophageal cancer and construction of prognosis prediction model: a retrospective cohort study[J]. Int J Surg, 2023, 109(6): 1708-1719.

[14] NAKAJO K, ABE S, ODA I, et al. Impact of the Charlson Comorbidity Index on the treatment strategy and survival in elderly patients after non-curative endoscopic submucosal dissection for esophageal squamous cell carcinoma: a multicenter retrospective study[J]. J Gastroenterol, 2019, 54(10): 871-880.

[15] RICE T W, ISHWARAN H, FERGUSON M K, et al. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer[J]. J Thorac Oncol, 2017, 12(1): 36-42.

[16] WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Digestive System Tumours[M]. 5th ed. Lyon: IARC Press, 2019.

[17] JOSEPH A, DRAGANOV P V, MALUF-FILHO F, et al. Outcomes for endoscopic submucosal dissection of pathologically staged T1b

esophageal cancer: a multicenter study[J]. Gastrointest Endosc, 2022, 96(3): 445-453.

[18] REZA J A, RAMAN V, VEKSTEIN A, et al. Implementation of staging guidelines in early esophageal cancer: a study of the society of thoracic surgeons general thoracic surgery database[J]. Ann Surg, 2023, 278(4): e754-e759.

[19] KRILL T, BALISS M, ROARK R, et al. Accuracy of endoscopic ultrasound in esophageal cancer staging[J]. J Thorac Dis, 2019, 11 (suppl 12): S1602-S1609.

[20] MOTOYAMA S, JIN M, MATSUHASHI T, et al. Outcomes of patients receiving additional esophagectomy after endoscopic resection for clinically mucosal, but pathologically submucosal, squamous cell carcinoma of the esophagus[J]. Surg Today, 2013, 43(6): 638-642.

[21] IKEDA A, HOSHI N, YOSHIZAKI T, et al. Endoscopic submucosal dissection (ESD) with additional therapy for superficial esophageal cancer with submucosal invasion[J]. Intern Med, 2015, 54(22): 2803-2813.

[22] SAEKI H, WATANABE M, MINE S, et al. Esophagectomy for superficial esophageal cancer after non-curative endoscopic resection[J]. J Gastroenterol, 2015, 50(4): 406-413.

[23] SMYTH E C, LAGERGREN J, FITZGERALD R C, et al. Oesophageal cancer[J]. Nat Rev Dis Primers, 2017, 3: 17048.

[24] MÖNIG S, CHEVALLAY M, NICLAUSS N, et al. Early esophageal cancer: the significance of surgery, endoscopy, and chemoradiation[J]. Ann N Y Acad Sci, 2018, 1434(1): 115-123.

[25] MINASHI K, NIHEI K, MIZUSAWA J, et al. Efficacy of endoscopic resection and selective chemoradiotherapy for stage I esophageal squamous cell carcinoma[J]. Gastroenterology, 2019, 157(2): 382-390.e3.

[26] KADOTA T, MINASHI K, WAKABAYASHI M, et al. Diagnostic yield of conventional endoscopy with endoscopic ultrasonography for submucosal invasion of superficial esophageal squamous cell carcinoma: a post hoc analysis of multicenter prospective confirmatory study (JCOG0508)[J]. Esophagus, 2021, 18(3): 604-611.

[27] NIHEI K, MINASHI K, YANO T, et al. Final analysis of diagnostic endoscopic resection followed by selective chemoradiotherapy for stage I esophageal cancer: jcog0508[J]. Gastroenterology, 2023, 164(2): 296-299. e2.

[28] MIYAZAKI T, MYOJIN M, HOSOKAWA M, et al. Endoscopic resection as an independent predictive factor of local control in patients with T1bN0M0 esophageal squamous cell carcinoma treated with chemoradiotherapy: a retrospective study[J]. Radiat Oncol, 2022, 17(1): 11.

[29] SONG B G, KIM G H, CHO C J, et al. Close observation versus additional surgery after noncurative endoscopic resection of esophageal squamous cell carcinoma[J]. Dig Surg, 2021, 38(3): 247-254.

[30] TANAKA T, UENO M, IIZUKA T, et al. Comparison of long-term outcomes between esophagectomy and chemoradiotherapy after endoscopic resection of submucosal esophageal squamous cell carcinoma[J]. Dis Esophagus, 2019, 32(12): doz023.

[31] NAITO S, YOSHIO T, ISHIYAMA A, et al. Long-term outcomes of esophageal squamous cell carcinoma with invasion depth of pathological T1a-muscularis mucosae and T1b-submucosa by endoscopic resection followed by appropriate additional treatment[J]. Dig Endosc, 2022, 34(4): 793-804.

[32] AKUTSU Y, KATO K, IGAKI H, et al. The prevalence of overall and initial lymph node metastases in clinical T1N0 thoracic esophageal cancer: from the results of JCOG0502, a prospective multicenter study[J]. Ann Surg, 2016, 264(6): 1009-1015.

[33] SAWADA K, KOTANI D, YUKAMI H, et al. Definitive chemoradiotherapy has comparable survival outcomes to esophagectomy in patients with clinical T1N0M0 esophageal squamous cell carcinoma: real-world data[J]. Int J Clin Oncol, 2022, 27(8): 1279-1288.

[34] HOLYOAKE D L P, SMYTH E C. Chemoradiotherapy or surgery for very early esophageal squamous cancer: can a nonrandomized trial give us the answer?[J]. Gastroenterology, 2021, 161(6): 1793-1795.

[35] YANG Y, SU Y, ZHANG X, et al. Esophagectomy versus definitive chemoradiotherapy for patients with clinical stage N0 and pathological stage T1b esophageal squamous cell carcinoma after endoscopic submucosal dissection: study protocol for a multicenter randomized controlled trial (Ad-ESD Trial) [J]. Trials, 2020, 21(1): 603.

［本文编辑］吴　洋