The efficacy of current-used risk factors for metastasis and the effectiveness of additional surgical resection in pT1b esophageal squamous cell carcinoma after endoscopic resection: A multi-institutional retrospective study in China

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Abstract

Purpose

ER-treated patients with pT1b ESCC were strongly recommended to receive additional treatments, mainly radical surgical resection (SR). In view of high morbidity and mortality of additional SR treatment, this recommendation remained open to debate. Herein, our research aimed to access the efficacy of current risk predictors for metastasis based on the histological findings in ER specimens, and the effectiveness of additional SR.

Methods

We conducted a retrospective study of ER-treated pT1b ESCC patients with (n = 42) and without (n = 124) additional SR from 2007 to 2018 in China. Lymph node metastasis & distant organ metastasis (LNM&DOM) reflecting the overall metastasis risk of ESCC after ER treatment were used. The relationships between clinicopathological parameters and metastasis were assessed. And Overall survival(OS) and progression-free survival (PFS) were also analyzed.

Results

Patients with submucosal invasion depth (SMI) $\geq 200\mu\text{m}$ didn't demonstrate significant difference in LNM&DOM and survival, as compared with those with SMI $< 200\mu\text{m}$. In ER alone group, patients with vertical margin (VM) (+) showed worse PFS than those with VM(-) (p = 0.008). More strikingly, for patients in low-risk group who had LVI(-) and VM(-), ER + SR didn't significantly prolong their PFS (p = 0.120) but significantly shorter their OS (p < 0.010) as compared with ER alone treatment.

Conclusions

SMI $\geq 200\mu\text{m}$ isn't a sensitive and predictive indicator for both LNM&DOM and survival for patients with ER treatment. More strikingly, additional SR is not an optimal therapeutic selection for ER-treated pT1b ESCC in low-risk group who had LVI(-) and VM(-).

Introduction

Endoscopic resection (ER) has become gold standard for the treatment of superficial esophageal squamous cell carcinoma (ESCC) due to safe, short recovery time and the preservation of esophagus, as compared with esophageal radical surgical resection (SR). Unfortunately, data from radical SR demonstrated that the incidence of lymph node metastasis (LNM) in ESCC with sm1, sm2 and sm3 invasion (superficial, middle and deep thirds of the submucosa, respectively) were 16.92%-24.0%, 13.73%-20.5% and 34.3%-43.8%, respectively (B Li, et al. 2013, Y Zhou, et al. 2016, Y Zhou, et al. 2019).

Meanwhile, data from ER revealed that the cumulative 5-year metastasis rates of ESCC with sm1 (submucosal invasion depth (SMI) < 200µm) and sm2 (SMI ≥ 200µm) were approximately 7.7% and 36.2%, respectively (T Yamashina, et al. 2013). Based on these data, ER-treated pT1b ESCC were strongly recommended to receive additional treatments for curative intent according to 2020 Japan Gastroenterological Endoscopy Society (JGES) guideline for esophageal cancer (R Ishihara, et al. 2020). However, given the evidence were largely originated from small-size retrospective studies, this recommendation remained open to debate. And this new recommendation seems to be more aggressive than the previous 2017 Japanese Esophageal Society (JES) guideline, which recommended patients with high-risk factors, SMI ≥ 200µm and/or lymphovascular invasion (LVI) (+), for additional treatment (S Japan Esophageal 2017).

In terms of curability, additional SR would be a better choice than ER. However, the occurrence of related complications, such as anastomotic leak and reflux, would increase correspondingly, and decrease the patient's long-term quality of life (Y Zhang, et al. 2019, Y Koterazawa, et al. 2018, H Saeki, et al. 2015). Moreover, based on stringent selection criteria in routine clinical practice, only patients without obvious LNM and deep invasion detected by preoperative imaging and endoscopic examinations underwent ER. Thus, less LNM can be expected in ER-treated patients than that in SR-treated patients (R Ishihara, et al. 2020, Y Zhang, et al. 2019). Therefore, ER-treated pT1b ESCC patients represents a distinct subgroup of patients with relatively less aggressive clinical course than those SR-treated counterparts.

Herein, our research conduct the largest study which enrolled 166 cases of pT1b ER-treated patients with or without additional SR, aiming to access the efficacy of current risk predictors for metastasis based on the histological findings in ER specimens, and the effectiveness of additional SR.

Materials And Methods

Patients

Initially, 173 cases of ER-treated pT1b ESCC from 2007 to 2018 without preoperative or postoperative radio chemotherapy were evaluated. They were diagnosed at National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital. Based on exclusion criterion, 124 cases were eventually included in ER group (Fig. 1).

Meanwhile, between 2007 and 2018, 62 cases of pT1b patients treated by ER followed by SR were initially selected from four hospitals. They all underwent two-field lymphadenectomy. According to exclusion criterion, we finally enrolled 42 cases for ER+SR group (Fig. 1), including National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital (n=20), Nanjing Drum Tower Hospital (n=8), Shanghai Zhongshan Hospital (n=8) and the Fourth Hospital of Hebei Medical University (n=6).

The exclusion criteria are as follows: 1) Combination with SCC of other sites, 2) Second primary ESCC, 3) Combination with other type of cancer, 4) Carcinoma with basaloid or spindle cell subtypes, 5) No follow-

up data, 6) Time of follow-up < 6 months, 7) Incomplete clinical data (e.g. no SMI depth value).

Clinicopathological evaluation and follow up

The clinicopathological variables in two cohorts were evaluated, including age, gender, tumor location, tumor poor differentiation (PD), LVI, and SMI.

More importantly, both synchronous and metachronous metastasis of lymph node and distant organ were integrated into the data of LNM&DOM (lymph node metastasis & distant organ metastasis) in order to reflect the overall metastasis risk of ESCC after ER treatment. Meanwhile, patients with follow-up time less than 6 months were excluded from our analysis.

Statistical Analysis

The baseline characteristics between ER alone and ER+SR treatment were analyzed by Chi-square test or Mann-Whitney test. The odd ratio (OR) for LNM&DOM of each parameter was calculated by univariate logistic regression analysis firstly, in which parameters with $p < 0.05$ were evaluated together using multivariate logistic regression analysis.

The times of overall survival (OS) and progression-free survival (PFS) were defined from the date of ER to the date of death/event or the last follow-up. The day of last follow-up was January 9st 2021. The survivals were compared by using Log-Rank and Cox regression analysis. The survival curve was plotted using Kaplan–Meier procedure.

All statistical analysis was two sided and $p < 0.05$ was defined as significance. All above statistical analyses were run in R 3.6.0 statistical software.

Results

The baseline characteristics of pT1b ER ESCC

The characteristics of ER-treated patients were summarized in Table 1. All of them were diagnosed as common squamous cell carcinoma, excluding basaloid or spindle cell subtypes. And all of them were confirmed as pT1b based on the ER specimens.

Table 1
The baseline characteristics of 166 cases of pT1b ESCC with endoscopic resection

		ER + SR	ER	<i>p_value</i>
		(n = 42)	(n = 124)	(Chi-squared test)
Age				
	Median [IQR]	60.5 [55.00, 64.00]	62 [57.00, 67.00]	0.101 [#]
Sex				
	Female	5 (11.9%)	31 (25.0%)	0.118
	Male	37 (88.1%)	93 (75.0%)	
Submucosal invasion depth ≥ 200μm				
	Negative	5 (11.9%)	33 (26.6%)	0.08
	Positive	37 (88.1%)	91 (73.4%)	
VM				
	Negative	32 (76.2%)	121 (97.6%)	< 0.001
	Positive	10 (23.8%)	3 (2.4%)	
LVI				
	Negative	29 (69.0%)	108 (87.1%)	0.015
	Positive	13 (31.0%)	16 (12.9%)	
PD				
	Negative	30 (71.4%)	72 (58.1%)	0.176
	Positive	12 (28.6%)	52 (41.9%)	
Location				
	Upper	7 (16.7%)	17 (13.7%)	0.319
	Middle	9 (21.4%)	42 (33.9%)	
	Lower	26 (61.9%)	65 (52.4%)	
LNM&DOM				

IQR, interquartile range; PD, poor differentiation; LVI, lymph-vascular invasion; VM, vertical margin; LN&DOM, lymph node metastasis & distant organ metastasis.

[#], Mann-Whitney test

	ER + SR	ER	<i>p_value</i>
	(n = 42)	(n = 124)	(Chi-squared test)
Negative	28 (66.7%)	113 (91.1%)	< 0.001
Positive	14 (33.3%)	11 (8.9%)	
IQR, interquartile range; PD,poor differentiation; LVI,lymph-vascular invasion; VM, vertical margin; LNM&DOM, lymph node metastasis & distant organ metastasis.			
# , Mann-Whitney test			

The incidences of LVI (31.1%) and VM(+)(23.8%) in ER + SR group were significantly higher than those in ER alone group. Accordingly, the rate of LNM&DOM in ER + SR group (33.3%) was nearly four times as many as that in ER alone group (8.9%).

Analysis Of Lnm&dom In Patients With Er + sr Treatment

In ER + SR group, VM ($p = 0.049$), LVI ($p = 0.002$), PD ($p = 0.006$) and number of resected lymph nodes($p = 0.021$) were significantly associated with LNM&DOM. However, based on multivariate logistic regression analysis, only LVI was an independent predictor for LNM&DOM ($p = 0.035$), as shown in Table 2.

Table 2
Logistic regression analysis for LNM&DOM in pT1b ER + SR specimens

	LNM&DOM		OR_U(95%CI)	p-value	OR_M(95%CI)	p-value
	Negative (n = 28)	Positive (n = 14)				
Age						
Median [IQR]	61 [58, 65]	58 [49, 62]	0.92(0.84–1.01)	0.078		
Sex						
Female	5 (100.0%)	0 (0.0%)				
Male	23 (62.2%)	14 (37.8%)	NA	NA		
Submucosal invasion depth $\geq 200\mu\text{m}$						
Negative	4 (80.0%)	1 (20.0%)	1			
Positive	24 (64.9%)	13 (35.1%)	2.17(0.22–21.46)	0.509		
VM						
Negative	24 (75.0%)	8 (25.0%)	1		1	
Positive	4 (40.0%)	6 (60.0%)	4.5 (1.01–20.11)	0.049	4.48(0.71–28.37)	0.112
LVI						
Negative	24 (82.8%)	5 (17.2%)	1			
Positive	4 (30.8%)	9 (69.2%)	10.8 (2.36–49.46)	0.002	6.76(1.15–39.9)	0.035
PD						
Negative	24 (80.0%)	6 (20.0%)	1			
Positive	4 (33.3%)	8 (66.7%)	8 (1.79–35.74)	0.006	2.87(0.46–17.96)	0.259
Location						
Upper	5 (71.4%)	2 (28.6%)	1			

NA, not applicable;

OR_U, Odd ratio by univariate analysis; OR_M, Odd ratio by multivariate analysis; IQR, interquartile range; PD, poor differentiation; LVI, lymph-vascular invasion; VM, vertical margin; LNM&DOM, lymph node metastasis & distant organ metastasis.

	LNM&DOM		OR_U(95%CI)	p_ value	OR_M (95%CI)	p_ value
	Negative (n = 28)	Positive (n = 14)				
Middle	7 (77.8%)	2 (22.2%)	0.714 (0.07–6.92)	0.772		
Lower	16 (61.5%)	10 (38.5%)	1.562 (0.25–9.65)	0.631		
Number of resected lymph nodes						
Median [IQR]	16.0 [13.0, 20.3]	22.5 [16.3, 31.5]	1.111 (1.02–1.22)	0.021	1.06(0.95–1.19)	0.270
NA, not applicable;						
OR_U, Odd ratio by univariate analysis; OR_M, Odd ratio by multivariate analysis;IQR, interquartile range; PD,poor differentiation; LVI,lymph-vascular invasion; VM, vertical margin; LNM&DOM, lymph node metastasis & distant organ metastasis.						

Analysis Of Lnm&dom In Patients With Er Alone Treatment

In ER alone group, none of the clinicopathological characteristics was correlated with LNM&DOM, as shown in Table 3.

Table 3
Logistic regression analysis for LNM&DOM in pT1b ER specimens

	LNM&DOM		OR_U(95%CI)	p_value
	Negative (n = 113)	Positive (n = 12)		
Age				
Median [IQR]	62[57, 67]	61 [58, 66]	0.994 (0.921–1.072)	0.870
Sex				
Female	29 (93.5%)	2 (6.5%)	1	
Male	84 (90.3%)	9 (9.7%)	1.554 (0.317–7.613)	0.587
Submucosal invasion depth $\geq$ 200μm				
Negative	31 (93.9%)	2 (6.1%)	1	
Positive	82 (90.1%)	9 (9.9%)	1.701 (0.348–8.317)	0.512
VM				
Negative	111 (91.7%)	10 (8.3%)	1	
Positive	2 (66.7%)	1 (33.3%)	5.55 (0.462–66.683)	0.177
LVI				
Negative	99 (91.7%)	9 (8.3%)	1	
Positive	14 (87.5%)	2 (12.5%)	1.571 (0.308–8.03)	0.587
PD				
Negative	68 (94.4%)	4 (5.6%)	1	
Positive	45 (86.5%)	7 (13.5%)	2.644 (0.732–9.558)	0.138
Location				
Upper	15 (13.3%)	2 (18.2%)	1	
Middle	41 (36.3%)	1 (9.1%)	0.183 (0.015–2.167)	0.178
Lower	57 (50.4%)	8 (72.7%)	1.053 (0.202–5.484)	0.951
OR_U, Odd ratio by univariate analysis; IQR, interquartile range; PD,poor differentiation; LVI,lymph-vascular invasion; VM, vertical margin; LNM&DOM, lymph node metastasis & distant organ metastasis.				

Analysis of PFS in patients with ER + SR and ER alone treatments

As to PFS, patients with PD(+) had shorter PFS than those with PD(-) in ER + SR group ($p = 0.022$), as shown in Table 4. More importantly, in ER specimens, patients with VM (+) showed worse PFS than those with VM(-) in ER alone group ($p = 0.008$), but no significant difference was found in ER + SR group ($p = 0.640$), as shown in Table 4.

Table 4
Cox regression analysis for PFS in ER + SR and ER alone groups

	ER + SR		ER alone	
	HR_U (95%CI)	p_value	HR_U (95%CI)	p_value
Age (median [IQR])	1.008 (0.909–1.117)	0.882	0.989 (0.926–1.056)	0.734 [#]
Sex = male	NA	NA	1.355 (0.377–4.863)	0.641
Submucosal invasion depth $\geq 200\mu\text{m}$	0.46 (0.048–4.43)	0.502	2.257 (0.505–10.088)	0.287
VM = Positive	0.598 (0.069–5.167)	0.640	7.621 (1.684–34.496)	0.008
LVI = Positive	2.271 (0.452–11.408)	0.319	2.164 (0.599–7.814)	0.239
PD = Positive	13.389 (1.464–122.456)	0.022	2.827 (0.973–8.21)	0.056
Location				
Middle	1.129 (0.063–20.304)	0.934	0.361 (0.051–2.567)	0.309
Lower	0.895 (0.095–8.412)	0.922	1.545 (0.338–7.067)	0.575
NA, not applicable; HR_U, hazard ratio by univariate analysis; PD, poor differentiation; LVI, lymphovascular invasion; VM, vertical margin; LNM&DOM, lymph node metastasis & distant organ metastasis.				

The comparisons of OS and PFS between ER alone and ER + SR treatment in low- and high-risk groups

Based on the status of LVI and VM, the patients were divided into low and high-risk groups. Patients with both LVI(-) and VM(-) were put into low-risk group, and patients with LVI(+) and/or VM(+) were selected in the high-risk group.

Herein, in low-risk group, patients with ER + SR treatment demonstrated significantly worse OS than those with ER alone treatment (81.8% and 98.0%, respectively, at 5 years; Log-Rank: $p < 0.010$). While, no significant difference in PFS was found between these two treatments (77.4% and 89.6%, respectively, at 5 years; Log-Rank: $p = 0.120$) (Fig. 2a).

However, in high-risk group, patients with ER alone treatment tend to have worse OS as compared with those with ER + SR treatment (80.8% and 100%, respectively, at 5 years), but the p-value didn't achieve statistical significance probably due to small sample size (Log-Rank: $p = 0.160$) (Fig. 2b). Moreover, no significant difference in PFS was found between these two treatments (Log-Rank: $p = 0.370$) (Fig. 2b).

In low-risk group, PD was significantly correlated with treatment ($p = 0.008$) (Table 5). Thus, in order to eliminate potential impacts by PD, we identified an extremely low-risk group with VM(-), LVI(-) and PD(-). And the results showed that patients with ER + SR treatment still had significantly worse OS than those with ER alone treatment (88.9% and 100.0%, respectively, at 5 years; Log-Rank: $P = 0.020$). While, no significant difference in PFS was found between these two treatments (90.9% and 92.7%, respectively, at 5 years; Log-Rank: $p = 0.890$) (Fig. 3).

Table 5
The baseline characteristics of patients in low-risk group with LVI(-) and VM(-)

Low-risk group	ER	ER + SR	p_value
	(n = 106)	(n = 23)	(Chi-squared test)
Age			
Median [IQR]	62 [57.00, 67.00]	60 [55.00, 65.00]	0.201 [#]
Sex			
Female	29 (27.4%)	4 (17.4%)	0.466
Male	77 (72.6%)	19 (82.6%)	
Submucosal invasion depth ≥ 200μm			
Negative	29 (27.4%)	5 (21.7%)	0.769
Positive	77 (72.6%)	18 (78.3%)	
PD			
Negative	63 (59.4%)	21 (91.3%)	0.008
Positive	43 (40.6%)	2 (8.7%)	
Location			
Upper	15 (14.2%)	6 (26.1%)	0.320
Middle	36 (34.0%)	8 (34.8%)	
Lower	55 (51.9%)	9 (39.1%)	
#, Mann-Whitney test			

Discussion

The presence of metastasis of lymph node and/or distant organ is an unfavorable prognostic factor for survival of ESCC. Estimating the probability of LNM&DOM in pT1 ESCC is crucial for further therapeutic selection after ER. In our study, the overall incidence of LNM&DOM was 15.1% (25/166). This result was in line with the study of Yamashina T, *et al.*, which showed 21.2% (11/52) for their overall risk of metastasis. Moreover, our study revealed that the rate of LNM&DOM in ER + SR group was significantly higher than that in ER alone group (33.3% vs. 8.9%, $p < 0.001$). This is mainly because patients who had high-risk factors in routine practice tend to receive aggressive additional SR, with the higher incidences of LVI (31.0%) and VM (+) (23.8%) in ER + SR group than those in ER alone group (Table 1).

Meanwhile, we were curious about the efficacy of current risk predictor for metastasis and survival based on the histopathological findings in ER specimens. LVI is a widely-accepted risk factor for metastasis in patients with ER (K Takahashi, *et al.* 2018). In our study, LVI was significantly associated with LNM&DOM in ER + SR group ($p = 0.035$), but not in ER alone group ($p = 0.587$) (Table 2 and Table 3). Patients with $\text{SMI} \geq 200\mu\text{m}$ didn't demonstrate significant difference in LNM&DOM and survival (Table 2, Table 3 and Table 4) as compared with those with $\text{SMI} < 200\mu\text{m}$. In the study of Yamashina T, *et al.*, ESCC with $\text{SMI} \geq 200\mu\text{m}$ demonstrated significantly higher metastasis and poorer survival as compared with those with epithelium/lamina propria mucosae invasion. But it didn't show significant difference as compared with those with $\text{SMI} < 200\mu\text{m}$, demonstrating overlap of their 95% CI ranges of hazard ratio (T Yamashina, *et al.* 2013). Part of the reasons for this phenomenon is that patients with too deep invasion were excluded from the ER treatment, leading to the shorter range of invasion depth in ER-treated cohort as compared to that in SR-treated counterparts. Therefore, $200\mu\text{m}$ may be not an optimal cutoff value for ER-treated pT1b patients to predict LNM&DOM and survival.

Moreover, in ER alone group, patients with VM (+) showed worse PFS than those with VM(-) ($p = 0.008$), indicating potential remnant cancers which could result in recurrence of disease, and, correspondingly, worse PFS (Table 4). More interestingly, in ER + SR group, VM(+) didn't predict the worse PFS ($p = 0.640$) anymore, suggesting that additional SR may overcome the adverse effect of VM (+) in ER specimens. Thus, even though the residual cancer in VM sometimes can be eliminated by burning effect, its risk assessment in routine practice should be performed cautiously.

In our study, we were curious about the effectiveness of additional SR for pT1b ESCC, especially for those with LVI(-) and VM(-). Strikingly, for patients in low-risk group who had LVI(-) and VM(-), ER + SR didn't significantly prolong their PFS as compared with ER alone treatment (77.4% and 89.6%, respectively, at 5 years; Log-Rank: $p = 0.120$) (Fig. 2a). But it demonstrated significantly shorter OS in ER + SR group than that in ER alone group (81.8% and 98.0%, respectively, at 5 years; Log-Rank: $P < 0.010$). These results strongly supported that patients in low-risk group could not get benefits from additional SR but harm of procedure-related complications or deaths (H Saeki, *et al.* 2015). And the results were similar in extremely low-risk group who had VM(-), LVI(-) and PD(-) (Fig. 3). Thus, additional SR after ER is not a reasonable option for these low-risk patients, avoiding overtreatment.

To the best of our knowledge, this is the largest study enrolling 166 cases of pT1b ESCC after ER to evaluate the efficacy of current-used risk factors and the effectiveness of additional SR. However, some statistical bias may be in our study, such as retrospective study, a relatively short follow-up period and a relatively small sample size, which requires further investigation.

In conclusion, based on our study, $SMI \geq 200\mu m$ was a less sensitive and predictive indicator for both LNM&DOM and survival for patients with ER treatment. More strikingly, for patients in low-risk group who had LVI(-) and VM(-), ER + SR didn't prolong their PFS but significantly shorten their OS as compared with ER alone treatment. Thus, additional SR is not an optimal therapeutic selection for low-risk group.

Declarations

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Authors' contributions: XX, QS, DJ, XW and YL contributed to data collection and clinical follow-up. XX contributed to data analysis and manuscript writing. CG, LL and NC contributed to data interpretation. GW, YL, YH, XF and LX contributed to study design, coordination, discussion and manuscript editing. All authors read and approved the final manuscript.

Ethics approval: Due to the retrospective study, the data regarding treatment and prognosis were acquired by means of medical record consultation and telephone conversation. Thus, the need for consent was waived by 1) the Independent Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences, National GCP Center for Anticancer Drugs (20/197-2393), 2) The Ethics Committee of Nanjing Drum Tower Hospital of Nanjing University Medical School (2020-254-02), 3) The Ethics Committee of Zhongshan Hospital of Fudan University (B2020-313) and 4) The Ethics Committee of the Fourth Hospital of Hebei Medical University (2020ky121).

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Figures

Figure 1

Flowchart of enrollment of patients

Figure 2

Comparisons of PFS and OS between ER alone and ER+SR treatment in low-risk group with LVI(-) and VM(-) (a) and high-risk group with LVI(+) and/or VM(+) (b)

Figure 3

Comparisons of PFS and OS between ER alone and ER+SR treatment in extremely low-risk group with LVI(-), VM(-) and PD(-)