

Additional endoscopic treatments for patients with positive lateral margins after endoscopic resection of early esophageal squamous cell carcinoma

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Received August 16, 2022; Accepted December 7, 2022

DOI: 10.3892/ol.2022.13653

Abstract. There are currently no well-established treatment strategies for early esophageal squamous cell carcinoma (ESCC) for patients with only positive lateral margin (LM+) following endoscopic resection (ER). The present study aimed to find a treatment strategy for patients with early ESCC with non-curative resection (non-CR) and only LM+ following ER. In total, 511 patients with early ESCC treated at the Fourth Hospital of Hebei Medical University (Shijiazhuang, China) with ER were retrospectively analyzed, 41 of which (8%) were patients with only LM+ after non-CR. Of these, 28 patients received re-ER and 13 received additional surgical treatment. The clinicopathological characteristics of patients were analyzed and those who underwent additional surgery vs. re-ER were compared. Residual cancer cells were found in 27 patients (27/41, 65.9%) following re-ER or additional surgery. A significant increase in residual cancer cells was observed in patients with poorly differentiated cancer and patients with multiple LM+ ($P=0.03$ and $P=0.015$, respectively). Older patients and patients with single LM+ tended to choose re-ER ($P=0.023$ and $P=0.038$, respectively). In addition, there were three cases (3/13, 23.1%) of lymph node metastasis in the additional surgery group. However, within the limited follow-up time (mean, 36.1 ± 24.1 months), no recurrence or metastasis was found in the remaining patients. The results showed that re-ER may be a more suitable additional therapy compared with surgery for patients with LM+ following non-CR, at least in the medium-term.

Introduction

Esophageal cancer is the seventh most common malignant tumor, ranking sixth in global cancer-associated mortality (1,2). In terms of histological subtypes, adenocarcinoma is commonly observed in Europe and the United States, whereas squamous cell carcinoma is the primary subtype in China (2,3). Early esophageal cancer is defined as cancer confined to the mucosa (T1a) or submucosa (T1b), regardless of the presence of lymph node metastasis (LNM) (4-6). In previous years, endoscopic treatment, namely endoscopic mucosal resection or endoscopic submucosal dissection (ESD), has been increasingly regarded as a treatment option for early esophageal cancer (7,8).

The proportion of early (T1) stage detection has increased due to the improvement of endoscopic detection (9). Endoscopic resection (ER) of early tumors is the first step in patient management (9,10). ER is curative in most types of intramucosal (T1a) cancer and cancer that partially invades the submucosa (T1b) (11). Esophagectomy with lymph node dissection is not clearly indicated as the first choice in patients with 'non-curative' or 'potentially curative' ER (11). Based on previous studies, esophagectomy results in a 5-10% mortality rate (12,13). However, due to high morbidity and mortality as a result of complications with esophagectomy, certain patients do not receive surgical treatment (14-17).

According to the guidelines of the European Society of Gastrointestinal Endoscopy, if there are poorly differentiated lesions, lymphovascular invasion (LVI) or positive vertical margins, further treatment is recommended (11). By contrast, the Japanese Gastroenterology Endoscopy Society recommends additional treatment for patients with submucosal infiltration following ER of esophageal cancer, but there is still no consensus on what to do in these cases (18). To date, adjuvant management following non-curative or high-risk ER is not standardized. Therefore, the present study aimed to propose an additional treatment strategy for patients with non-curative resection (non-CR) and only positive lateral margin (LM+) following ER of early esophageal squamous cell carcinoma (ESCC).

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Key words: early esophageal squamous cell carcinoma, endoscopic resection, non-curative resection, positive lateral margin

Materials and methods

Patients. The present study retrospectively analyzed 511 patients (31-85 years) with early ESCC who underwent ER in the Fourth Hospital of Hebei Medical University (Shijiazhuang, China) from January 2000 to June 2022, of whom 84 had non-CR. The baseline characteristics, methods of endoscopic treatment and histological features in the medical records were reviewed.

The study included only patients with LM+ and non-CR (n=41). The exclusion criteria were as follows: i) Positive deep margin; ii) incomplete resection; iii) previous history of esophageal cancer; iv) additional history of chemotherapy or radiotherapy and v) clinical observation without additional treatment (Fig. 1). All patients provided written informed consent. The present study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (2020YB318).

Complete resection was defined as en bloc resection with margins macroscopically and microscopically free of tumor. Incomplete resection was defined as the presence of cancer cells in the lateral (anterior, posterior, proximal or distal) and deep margin. CR was achieved when a resected specimen met the requirements of complete resection without submucosal invasion or LVI. If the resection did not meet the criteria of CR, it was defined as non-CR (19-21). LM+ was defined as cancer cells histologically apparent in the LMs of the dissected specimens. Single LM+ referred to one direction (anterior, posterior, proximal or distal) of invasion and multiple LM+ to >2 directions. In addition, residual cancer was defined as the presence of cancer cells in pathological specimens following additional surgery or re-ER.

Endoscopic procedure and follow-up. Endoscopic treatment and follow-up were performed as previously described (22). For re-ER, Lugol's iodine staining was used to evaluate lesion size. Argon plasma coagulation (FiAPC® probes were used for the flexible endoscope; ERBE Elektromedizin GmbH) was used to mark ~5 mm outside the boundary of the lesion (22). This was the resection range of re-ER.

Histopathological evaluation. Endoscopically resected specimens were serially sectioned at 2 mm intervals. The protocol for detailed histopathological evaluation was as previously described (22).

Additional treatment following ER. Of the 41 patients who received ER, 13 (31.7%) underwent additional surgery and 28 (68.3%) underwent re-ER. The clinicians chose re-ER or additional surgery after evaluating the clinical and pathological factors of each patient (from inspecting the final pathology report and the patient condition), which included age, underlying disease and consent to additional surgery. Patients who refused additional treatment underwent close observation. Due to lack of consensus in the literature, the final choice of treatment was based on the doctor's evaluation (11,18). Re-ER and additional surgery were performed <3 months or 1 month following initial ER, respectively.

Statistical analysis. Categorical variables were analyzed using χ^2 or the Fisher's exact test. Continuous variables are reported

Table I. Baseline clinicopathological characteristics of patients.

Characteristic	Number of patients
Sex	
Male	24
Female	17
Age, mean \pm SD, years	64.5 \pm 8.5
Tumor location	
Upper esophagus	2
Middle esophagus	25
Lower esophagus	14
Tumor size, cm	
<2.5	16
\geq 2.5	25
Treatment method	
EMR	13
ESD	28
Resection state	
En bloc	33
Piecemeal	8
WHO classification	
Well-differentiated	15
Moderately differentiated	16
Poorly differentiated	10
Final pathology	
No residual cancer	14
Residual cancer	27
Lateral margin multiplicity	
Single	28
Multiple	13

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SD, standard deviation; WHO, World Health Organization.

as median and range or mean \pm standard deviation and were compared using Student's t or the Mann-Whitney U test. $P < 0.05$ was considered to indicate a statistically significant difference. All analyses were performed using SPSS version 19.0 (IBM Corp.).

Results

Clinicopathological features of patients. The mean age of all patients was 64.5 \pm 8.5 years. Table I summarizes the baseline clinicopathological characteristics of patients with non-CR who were only LM+ following ER of early ESCC. There were 28 patients (68.3%) with single LM+ and 13 patients (31.7%) with multiple LM+. Following additional surgery or re-ER, 27 resected specimens (65.9%) showed residual cancer.

Comparison of additional treatment methods after ER. A comparison of the two additional treatment methods following non-CR is shown in Table II. The mean age of patients in the re-ER group was higher than that in the surgery group

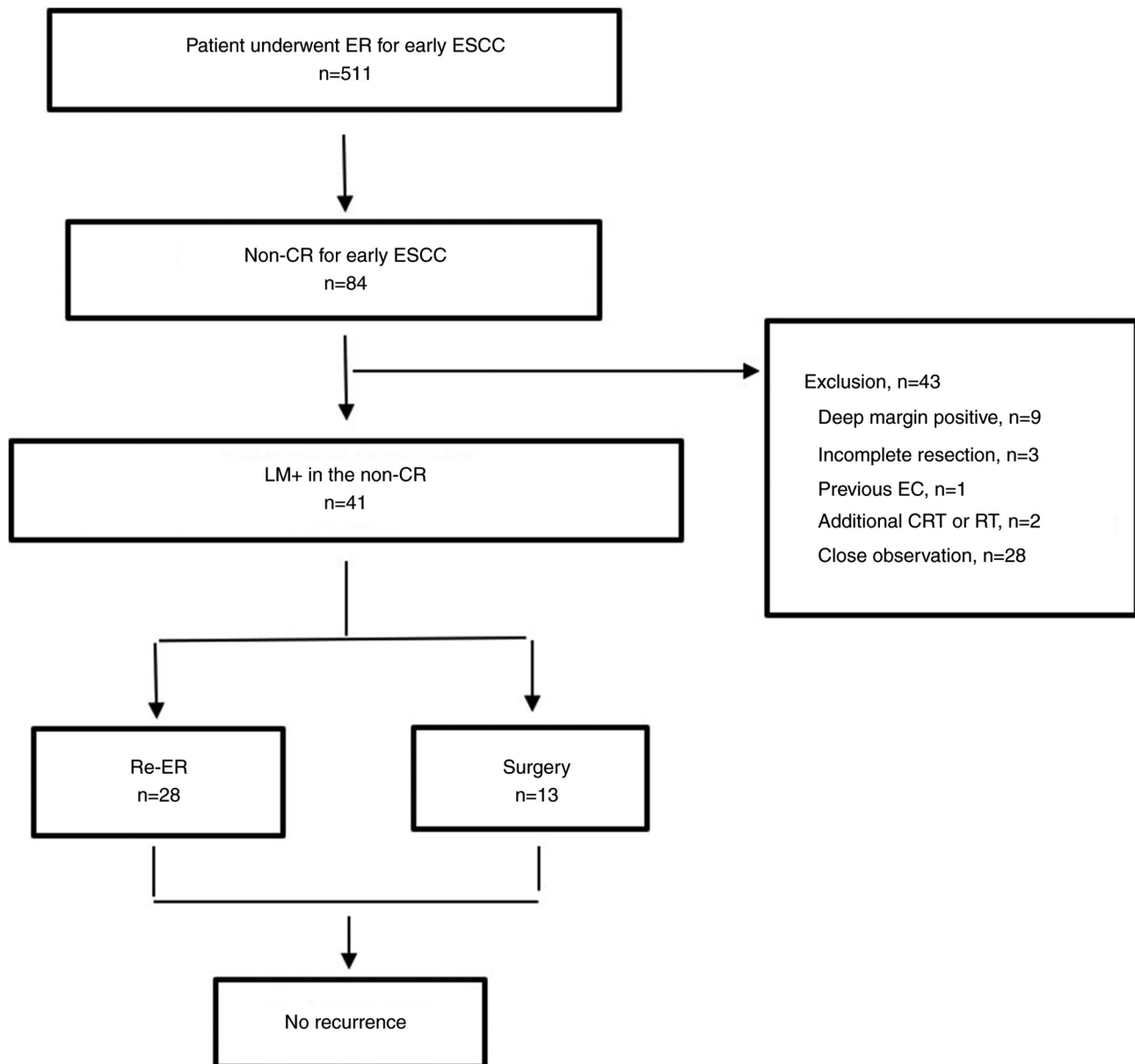


Figure 1. Flowchart of patients with LM+ after ER of early ESCC. CRT, chemoradiotherapy; EC, esophageal carcinoma; ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; LM+, positive lateral margin; non-CR, non-curative resection; RT, radiotherapy.

(69.5±9.5 vs. 62.5±7.8 years; $P=0.023$). Patients with multiple LM+ after ER were most often treated with surgery (re-ER (n=28), 21.4% vs. surgery (n=13), 53.8%; $P=0.038$). Patients with well-differentiated lesions were more likely to receive re-ER than additional surgery ($P=0.003$). Residual cancer was more common in the additional surgery group but there was not a statistically significant difference (re-ER (n=28), 60.7% vs. surgery (n=13), 76.9%; $P=0.308$). There were also no statistically significant differences between the two groups in terms of sex, tumor location, size, tumor shape or residual cancer at final pathology.

Pathological features of residual lesions following additional treatment after ER. Table III lists pathological features of residual lesions following non-CR (only LM+) with re-ER and additional surgery. In patients with poorly differentiated cancer, the proportion of residual cancer cells increased

significantly (No residual cancer (n=14), 14.3% vs. Residual cancer (n=27), 29.6%; $P=0.030$). Residual cancer was also significantly higher in the multiple LM+ group than in the single LM+ group (single LM+, 7.1% vs. multiple LM+, 44.4%; $P=0.015$).

Clinical results of additional treatments after ER. The mean follow-up time of all enrolled patients was 36.1±24.1 months. At the time of writing, there had been no recurrence, although in the additional surgery group, two patients had anastomotic leakage and one patient had respiratory failure.

Clinicopathological features of patients with additional surgery. The clinicopathological characteristics of 13 patients who underwent additional surgery are shown in Table IV. Among these 13 patients, LNM was present

Table II. Comparison of additional treatment following ER for early esophageal squamous cell carcinoma.

Characteristic	Re-ER, n=28	Surgery, n=13	P-value
Age, mean \pm SD, years	69.5 \pm 9.5	62.5 \pm 7.8	0.023
Sex, n			0.756
Male	18	9	
Female	10	4	
Tumor location, n			0.830
Upper esophagus	1	1	
Middle esophagus	17	8	
Lower esophagus	10	4	
Tumor size, mean \pm SD, mm	26.2 \pm 12.6	27.1 \pm 10.8	0.059
Tumor shape, n			0.781
Elevated	9	3	
Flat	12	7	
Depressed	7	3	
WHO classification, n			0.003
Well-differentiated	10	5	
Moderately differentiated	15	1	
Poorly differentiated	3	7	
Final pathology, n			0.308
No residual cancer	11	3	
Residual cancer	17	10	
Lateral margin multiplicity, n			0.038
Single	22	6	
Multiple	6	7	

Re-ER, re-endoscopic resection; SD, standard deviation; WHO, World Health Organization.

Table III. Pathological features of residual lesions following additional treatment post-endoscopic resection.

Pathological feature	No residual cancer, n=14	Residual cancer, n=27	P-value
Tumor size, mean \pm SD, mm	26.1 \pm 11.8	26.6 \pm 10.9	0.779
Tumor shape, n			0.862
Elevated	3	4	
Flat	6	13	
Depressed	5	10	
Lateral margin multiplicity, n			0.015
Single	13	15	
Multiple	1	12	
WHO classification, n			0.030
Well-differentiated	9	6	
Moderately differentiated	3	13	
Poorly differentiated	2	8	

WHO, World Health Organization.

in three cases (23.1%). There was no significant difference between the LNM and non-LNM subgroups in terms of age, sex or tumor location, size, shape, circumference or differentiation.

Discussion

With the advancement of endoscopic equipment, ER has been widely used to treat early esophageal cancer (23,24).

Table IV. Factors associated with LN metastasis in the esophagectomy group.

Characteristic	LN metastasis		P-value
	Present, n=3	Absent, n=10	
Age, mean \pm SD, years	63.5 \pm 8.8	62 \pm 6.9	0.889
Sex, n			0.913
Male	2	7	
Female	1	3	
Tumor location			0.850
Upper esophagus	0	1	
Middle esophagus	2	6	
Lower esophagus	1	3	
Tumor size, mean \pm SD, mm	27.6 \pm 11.8	28.1 \pm 9.1	0.563
Tumor shape			0.550
Elevated	1	2	
Flat	2	5	
Depressed	0	3	
Tumor circumference relative to esophageal lumen			0.701
<1/4	0	1	
1/4-3/4	3	8	
\geq 3/4	0	1	
WHO classification, n			0.084
Well-differentiated	0	5	
Moderately differentiated	1	0	
Poorly differentiated	2	5	

LN, lymph node; SD, standard deviation; WHO, World Health Organisation.

Moreover, ER has been shown to be effective for early esophageal cancer and can be used to histologically evaluate submucosal infiltration and LVI (7,8). This can help decide whether to recommend additional treatment following radical (R0) ER. ER is mostly curative in early esophageal cancer (11). However, the best adjuvant treatment methods following non-CR are still unclear (11,18), so subsequent curative treatment strategies need to be established. Xu *et al* (25) found that repeated esophageal ESD provides an alternative choice for recurrent superficial ESCC but did not assess early repeated ESD immediately following non-CR (confirmed pathologically). The focus of the present study was to propose treatment strategies for patients with only LM+ following non-CR.

Previous studies have shown that, when considering the age and complications (diabetes, cardiovascular and cerebrovascular diseases) of patients, additional ER is an option for patients with non-CR, as the overall survival rate and incidence of adverse events of these patients are not significantly different from those of patients undergoing surgery (26,27). Toya *et al* (28) recommended close follow-up as an alternative to surgery as there was no difference in the cancer-specific survival rate between the patients in these two groups (close follow-up or surgery) of their study. Additional surgical treatment after non-CR considering patient age and complications is controversial (27). Similarly, the present study found that older patients were more likely to choose re-ER as subsequent therapy. Due to perioperative risks

and/or short life expectancy, old age is an important reason for forgoing additional surgery following non-CR (29-31). The aforementioned studies suggested that older patients choose conservative treatment over surgical treatment.

In the research of gastric cancer, certain scholars have found that the poorer the differentiation type, the more directions of invasion the tumor has and the total length of LM affected by the tumor is significantly associated with a non-CR of residual tumor caused by LM+ (32-35). Similarly, in the present study, in patients with non-CR of ESCC, residual cancer was more common when there was a poorly differentiated histology and multiple LM+.

Certain studies have shown that patients with ESCC and deep mucosal infiltration (pT1a-m3), submucosal involvement (pT1b-m1-3) or LVI are considered to be at high risk of LNM and esophagectomy and lymph node dissection are recommended (36,37). However, in other studies, the incidence of LNM in esophageal resection specimens is 0-30%, the perioperative mortality rate is 0-14% and the incidence of serious complications is 26-43% (13,38-43). These findings are consistent with the results of the present study. In the present study, three patients who underwent additional surgery (3/13, 23.1%) had serious complications. Therefore, the present results do not support recommendations for additional surgery.

In addition, three patients (3/13, 23.1%) had LNM. Searching for accurate risk factors for LNM will help to

determine whether additional surgical treatment is needed. Previous studies have shown that surgery is not the best option for patients with early esophageal cancer whose ER is non-curative (44,45). Most notably, esophagectomy with lymphadenectomy cannot prevent tumor recurrence and the 5-year survival rate of T1N1 esophageal cancer following esophagectomy is <40% (46,47). Therefore, organ preservation strategy in the management of patients with early esophageal cancer has been implemented in daily clinical practice when patients refuse or are not suitable for surgery, but evaluation of whether other alternatives can bring greater benefits is needed. The positive margin may serve a role in patient prognosis (22) but a more detailed prognostic analysis needs to be confirmed by a multicenter study with long-term follow-up.

The present study investigated the optimal treatment strategy of only LM+ ESCC with non-curative ER. Younger patients with multiple LM+ and poorly differentiated histological lesions often chose additional surgical treatment. By contrast, older patients with single LM+ involvement and well-differentiated lesions were more likely to receive re-ER. There was no recurrence or metastasis in patients who received re-ER during the limited follow-up period (36.1±24.1 months) of the study. These results suggested that additional endoscopic treatment for patients with only LM+ following ER may be sufficient to remove residual tumors. Although some scholars have suggested that ER combined with radiotherapy and chemotherapy may be effective (48,49), the present study did not include patients who had received radiotherapy and chemotherapy so similar conclusions cannot be made.

The present study had certain limitations. Firstly, it was retrospective and single center, the number of cases was small and other endoscopic treatments (such as argon plasma coagulation and laser, photodynamic and microwave coagulation therapy) were not involved. Further studies on endoscopic treatment is required to conclude whether ER is useful. Secondly, the follow-up time was short, which may lead to bias in judging recurrence and metastasis of these patients. A multicenter long follow-up study is needed to verify the results of the present study. Thirdly, additional surgery was performed more often in patients with poor prognosis and/or multiple LM+, thereby potentially affecting the results.

In conclusion, re-ER may be adequate for patients with only LM+ and non-curative ER, especially older patients and those for whom surgical treatment is not recommended. This strategy is feasible, at least in the medium-term. Further studies, including large-scale, population-based, multicenter and prospective studies, should be conducted to evaluate additional endoscopic treatment strategies for patients with LM+ early ESCC after non-curative ER.

Acknowledgements

Not applicable.

Funding

The present study was supported by The Key Topics of Medical Science Research of Hebei Provincial Health Commission (grant no. 20190765).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YF and BQL designed the study. YF and SG confirm the authenticity of all the raw data. YF and WW collected clinical and pathological data of patients. SG and YF analyzed the data. BQL and WW contributed to the interpretation of results. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All patients agreed to participate in the present study and signed an informed consent form. The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (2020YB318) (Shijiazhuang, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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