Associated risk factor analysis and the prognostic impact of positive resection margins after endoscopic resection in early esophageal squamous cell carcinoma

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Abstract. Endoscopic resection for early esophageal cancer has a risk of residual margins. The risk these residual margins pose have not been fully evaluated. The present study aimed to investigate the associated risk factors and prognosis of residual margins following the endoscopic resection of early esophageal squamous cell carcinoma. In total, 369 patients (381 lesions) with early esophageal squamous cell carcinoma treated in the Fourth Hospital of Hebei Medical University (Shijiazhuang, China) with endoscopic resection were retrospectively analyzed. Sex, age, location, tumor diameter, depth of tumor invasion, endoscopic treatment, endoscopic ultrasonography (EUS) before resection, work experience of endoscopists and the degree of tumor differentiation were all evaluated as potential risk factors. In addition, the prognosis of patients with positive margins were analyzed. A total of 73 patients (73/381, 19.2%) had positive margins after endoscopic resection. Amongst the 65 patients who were successfully followed up, five patients succumbed to cardiovascular and cerebrovascular diseases, one patient received radiotherapy, two patients received radiotherapy and chemotherapy whilst one patient received chemotherapy. By contrast, 12 patients received surgery and 20 patients received additional endoscopic mucosal resection or endoscopic submucosal dissection. The other 29 patients were followed up regularly and no recurrence could be found. Univariate analysis revealed that tumor diameter, endoscopic treatment, depth of invasion, EUS before resection, degree of tumor differentiation and direction of invasion were all associated with the positive margin. Multivariate logistic regression analysis then found that EUS before resection, degree of tumor differentiation and depth of tumor invasion are independent risk factors for positive margins after endoscopic resection. These results suggest that poorly differentiated lesions and deeper invasion depth can increase the risk of positive margin after endoscopic resection. As a result, EUS evaluation before resection may reduce the risk of invasion depth. In addition, for poorly differentiated lesions, more aggressive treatment regimens may be recommended for preventing recurrence.

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Introduction

Esophageal cancer is a common type digestive system malignancy and currently ranks sixth in terms of the rate of cancer-associated mortality worldwide (1). Despite progress in the development of novel treatment strategies, the 5-year survival rate of esophageal cancer remains <20% (2). Esophageal cancer in the early stages is confined to the mucosa or superficial submucosa and accounts ~20% of all types of esophageal cancers (3). Surgical resection has long been the standard treatment method for early esophageal cancer (4). However, the high incidence of complications (such as gastroesophageal reflux and respiratory failure) as a result of this technique renders it unattractive, due to its severe negative effects on the quality of life of patients (4). Nevertheless, the development of gastroscopy has greatly improved the quality of life of patients with early esophageal cancer.

As advancements in endoscopic technology are made continuously, endoscopic resection is becoming the standard, minimally invasive treatment procedure for early esophageal cancer (5-7). It has been found to shorten the length of hospital stay and reduce the incidence of complications without affecting the quality of life, compared with those after esophagectomy (5-7).

However, similar to traditional esophagectomy, endoscopic resection also has the risk of a positive margin (positive margin refers to the presence of atypical cells at the lateral or deep resection margins). Positive margin after the endoscopic resection of early esophageal carcinoma has direct implications on the choice of treatment and disease prognosis (8). To date, previous studies of patients with early esophageal cancer (9-11) after undergoing endoscopic submucosal dissection (ESD) have produced sporadic results based on a small number of cases. Amongst the available reports on positive

margins, there are no reports of multicenter, large-sample trials with long-term follow-up periods.

Therefore, to explore methods of improving the prognosis of patients after the endoscopic resection of esophageal cancer, the present study investigated the potential risk factors for positive margins by comprehensively analyzing clinical and pathological data.

Materials and methods

Patients. The present study retrospectively analyzed the clinical, endoscopic and pathological data of patients with esophageal mucosal lesions treated with endoscopic resection in the Fourth Hospital of Hebei Medical University (Shijiazhuang, China) from January 2011 to December 2020.

The inclusion criteria of the lesions were as follows: i) Complete resection of lesions; ii) pathological diagnosis after endoscopic treatment was atypical cells (cells that looked different and function differently than normal) [low-grade intraepithelial neoplasia (LIN), high-grade intraepithelial neoplasia (HIN) or invasive cancer]; and iii) patients provided informed consent. The exclusion criterion was patients who were pathologically diagnosed with adenocarcinoma or inflammation after endoscopic treatment. Of note, intraepithelial neoplasia was defined as the neoplastic change before epithelial invasion, which can be divided further into 'low-grade' and 'high-grade' according to whether the structural and cytological abnormalities observed occupy the upper part of the epithelium (12).

A total of 369 patients (381 lesions) received endoscopic resection due to early esophageal carcinoma. Of these, 236 were males and 133 were females with a mean age of 63.5±9.9 years. The main clinical symptoms were retropharyngeal asphyxia and retrosternal pain. No other symptoms or findings could be observed during physical examination. All patients and their relatives were aware of the risks and benefits of endoscopic resection, following which written informed consent was obtained from all participants. The present study was approved by the Ethics committee of the Fourth Hospital of Hebei Medical University (Shijiazhuang, China).

Endoscopic treatment and pathological examination. Under the guidance of endoscopy, two treatment methods were used to remove the tumor: Endoscopic mucosal resection (EMR) and ESD.

Endoscopy-guided surgery. The type of endoscopic treatment performed in the present study was by professionally trained endoscopists using a single-channel endoscope (Olympus H260; Olympus Corporation). Argon plasma coagulation (APC; APC probes for flexible endoscope; Erbe Elektromedizin GmbH) was used to mark ~5 mm outside the boundary of the lesion. After fully marking the border, an epinephrine-containing hypertonic saline solution was injected into the submucosa for submucosal lifting. A circumferential mucosal incision was then created around the marking spots. In cases where the EMR technique was used, asymmetrical polypectomy snare (MTW Endoskopie) resection was initiated. For ESD, the submucosal layer was dissected using the IT-knife2 (KD-611L; Olympus Corporation). After the lesions were resected, the wounds were closed with APC, hot biopsy forceps coagulation or using titanium clips according to the wound conditions (Fig. 1A and B). The lesion was completely removed *en bloc* (Fig. 1C). The pathologist then evaluated tumor involvement in the lateral or deep resection margin (Fig. 1D).

Post-operative pathological examination. The resected specimens were processed and fixed immediately, before the lesion size was measured. After fixation with 10% formalin (20-25˚C for 12-24 h), the specimens were sent for pathological examination. The samples were cut into continuous sections at 2-mm intervals from top to bottom and embedded in paraffin. In total, three sections were prepared from each tissue and then stained with hematoxylin and eosin using the Ventana HE 600 automatic staining machine (Roche Diagnostics; 20-25˚C). An experienced pathologist (Dr Yao Liu, Department of Pathology, Fourth Hospital of Hebei Medical University) then used a light microscope (DM1000; Leica Microsystems GmbH; magnification, x200) to evaluate tumor involvement in the lateral or deep resection margin to avoid misjudgment. When examining the tissue sections for pathological evaluation, all sections were observed from the top of the tissue to identify the nature of the lesion, the degree of tumor differentiation, whether the vertical/transverse edge of the tumor was positive and whether there was vascular infiltration. A positive resection margin as defined as the presence of atypical cells (LIN, HIN or invasive cancer) at the lateral or deep resection margin.

Statistical analysis. Sex, age, lesion location, tumor diameter, depth of invasion, endoscopic treatment, endoscopic ultrasonography (EUS) before resection, working experience of the endoscopist and degree of tumor differentiation were all analyzed as potential risk factors.

Continuous data are presented as the mean ± standard deviation. χ^2 and nonparametric Mann-Whitney U tests were used for statistical analysis. Univariate and multivariate logistic regression models were used to examine the association between the variables and positive margins risk factors. $P<0.05$ was considered to indicate a statistically significant significance. The SPSS vl9.0 (IBM Corp.) was used for data processing.

Results

General data. The present study was a retrospective analysis of the data collected from 369 patients with early esophageal cancer who met the inclusion criteria. Among all study participants, 236 were male and 133 were female with a ratio of 1.8:1. The average age was 63.5±9.9 (range, 31-85) years.

Residues at the resection margin and follow-up data. In total, 73 patients had positive margin, such that the positive rate was 19.2%, where 64 (16.8%) were positive for lateral margins and nine (2.4%) were positive for vertical margins. In addition, it was found that the residual rates of EMR and ESD were 26.9 and 16.7%, respectively. Only 7.5% (23/308) poorly differentiated lesions were diagnosed in negative margins. By contrast, the proportion of positive margin specimens was

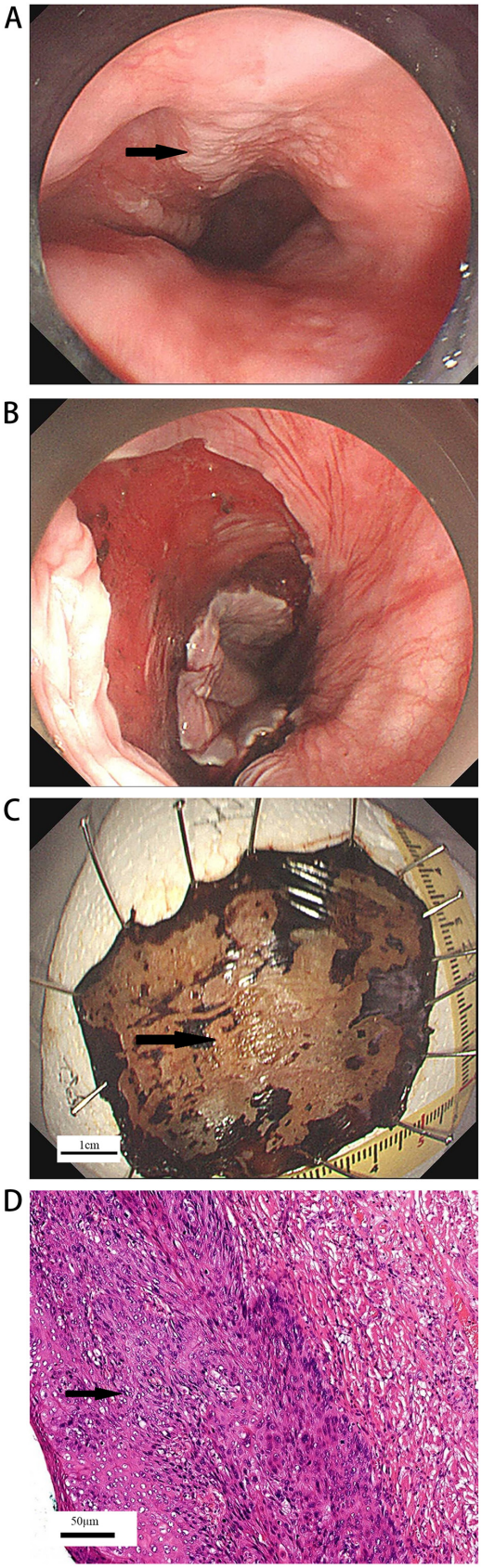

Figure 1. Endoscopic resection procedure for early esophageal squamous cell cancer. (A) Upper gastrointestinal endoscopy revealed a lesion located at the middle esophagus (the lesion is indicated by arrows). (B) Upper gastrointestinal endoscopy image of the esophagus after endoscopic resection. (C) En bloc image of the resected specimen, 6x4 cm (the lesion was indicated by arrows). (D) High-grade intraepithelial neoplasia in the deep resection margin as shown by H&E staining. The lesion was indicated by arrows. Magnification, x200.

28.8% (21/73). There was no vascular invasion or submucosal lymphatic metastasis. After communicating with the patients and their families, 29 patients asked for regular follow-up, while others with positive margins received another ESD or EMR and were followed up 1 month after operation. During the follow-up period, endoscopy was performed 3, 6 and 12 months after endoscopic resection, before being performed every year thereafter. Chest CT was also performed 6 and 12 months after endoscopic resection followed by once a year thereafter as a precaution for distant metastasis. Follow up was halted 5 years after endoscopic resection. If tumor cells were found at the edge of the deep resection, additional esophagectomy or esophageal radiotherapy and chemotherapy would be performed. These treatment options were selected according to the situation of each patient and the wishes of patients and their families. In the present study, 65 cases of residual tumors were successfully followed up for 2-60 months, with an average follow-up time of 28.1±10.1 months. The follow-up rate was 89%. However, eight patients were lost to follow-up. During the follow-up, five patients succumbed to cardiovascular and cerebrovascular diseases, whilst the other 60 patients remained alive during the follow-up period.

Comparison of groups with or without residual margins. A number of associated factors can affect the residual margin, including sex, age, lesion location, tumor diameter, depth of invasion, endoscopic treatment, EUS before resection, working experience of the endoscopist and degree of tumor differentiation (12). Univariate and multivariate analyses were performed to determine if any of these factors can affect the residual margin after endoscopic resection. As shown in Table I, there was no significant difference in sex, age, lesion location or working experience of endoscopists in the univariate analysis of incision margins. By contrast, tumor diameter, endoscopic treatment, depth of invasion, EUS before resection and the degree of tumor differentiation were all risk factors for residual margins. To exclude any confounding factors, multivariate logistic regression analysis (Table II) was performed. Only the depth of tumor invasion, degree of differentiation and EUS before resection were regarded to be risk factors for residual margins.

Discussion

Applications of EMR and ESD are becoming increasingly common for the treatment of early esophageal cancer (7). Endoscopic resection is able to not only preserve the integrity of the esophagus, but also circumvent the considerable risk of morbidity and mortality associated with esophageal resection (13). Previous studies have reported that although the effect of endoscopic resection on early esophageal cancer is equivalent to that of surgical resection, a lower incidence of complications and superior quality of life was associated with endoscopic resection (5,7). Several cohort studies (14-17) have recommended the use of EMR or ESD for T1a esophageal tumors, including highly atypical hyperplasia, adenocarcinoma or squamous cell carcinoma, which are limited to the superficial mucosa and do not extend to the muscular mucosa. In addition, Manner *et al* (18) have evaluated the efficacy and safety of endoscopic resection

Table I. Comparison of the groups with and without post-endoscopic resection residues at resection margins.

Parameter	Residues at resection margin (n=73)	No Residues at resection margin (n=308)	P-value
Age (years)	64.8±8.9	60.9±11.4	0.891
Sex			0.435
Female	23	112	
Male	50	196	
Location			0.136
Upper	3	23	
Middle	42	201	
Lower	28	84	
Tumor diameter			<0.001
≤1 cm	2	29	
1.1-3 cm	28	190	
>3 cm	43	89	
Endoscopic treatment methods			0.03
Endoscopic mucosal resection	25	68	
Endoscopic submucosal dissection	48	240	
Endoscopic ultrasonography evaluation before resection			<0.001
Yes	42	257	
No	31	51	
Working experience			0.673
≥5 years	45	198	
<5 years	28	110	
Depth of invasion			<0.001
Intramucosal cancer (M1)	30	208	
Lamina propria (M2)	11	33	
Muscularis mucosa (M3)	9	45	
Shallow and deep submucosal layer (SM1-2)	23	22	
Differentiation			<0.001
Well	23	233	
Moderate	29	52	
Poor	21	23	

Table II. Results of multivariate logistic regression analysis.

Parameter	P-value	Odds ratio	95% Confidence interval
Age	0.820	1.051	0.686-1.610
Sex	0.437	0.763	0.385-1.510
Maximum diameter of resected specimen	0.39	1.325	0.698-2.515
Location	0.663	1.187	0.549-2.564
Endoscopic resection procedures	0.526	0.774	0.350-1.710
Depth of tumor invasion	<0.001	2.182	1.704-2.795
Work experience	0.155	0.624	0.325-1.196
Degree of tumor differentiation	0.018	0.451	0.166-1.224
Endoscopic ultrasonography before resection	<0.001	35.826	7.400-173.454

in selected cases with mucosal myometrial infiltration and upper third submucosal involvement. These studies further verified the application of endoscopic resection in early esophageal cancer.

After the endoscopic resection of early esophageal cancer, the positive rate of resection edge varies greatly according to the literature, ranging 1.7-22% (9-11). In the present study, observation of atypical cells (including LIN, HIN or invasive cancer) at the resection margin was used as the criteria, where the positive rate of the resection margin was 19.2%. If only invasive cancer was considered, the positive rate of the resection edge then decreases to 5.4%. Previous studies have found that ESD has a higher *en bloc* resection and complete resection rates compared with those following traditional EMR (19-21). This finding is consistent with results from the present study, which found that the residual rates of EMR and ESD were 26.9 and 16.7%, respectively. However, based on logistic regression analysis, endoscopic resection was not found to be an independent risk factor, which is consistent with the results of Sgourakis *et al* (22). This finding may be associated with the results of retrospective analysis and not to the results of randomized controlled trials.

Over recent years, an increasing number of gastroenterologists in China consider ESD to be the optimal choice for the treatment of early esophageal cancer (23,24). They believe that with continuous advancements in ESD, the incidence of serious complications, such as perforation and bleeding, can be controlled to negligible levels (23-25). These studies further confirm that ESD is safe and effective in the treatment of early esophageal cancer.

Isomoto *et al* (26) previously reported that tumor size had no significant association with curative resection. However, the tumor size was significantly associated with segmental resection, where the cure resection rate was significantly lower compared with that of whole resection (26,27). In the present study, univariate analysis revealed that the maximum diameter of the primary tumor was associated with residual margin, but not in the multivariate analysis, which may be due to the nonrandomized endoscopic treatment methods (EMR and ESD) in the present retrospective analysis. In addition, the present study found that preoperative EUS examination and depth of tumor invasion are independent risk factors for residual resection margin. Previous studies have shown that EUS is the optimal noninvasive tool for T1 esophageal cancer, with a sensitivity of 85% and a specificity of 87% (28,29). This finding was also illustrated in previous studies of gastrointestinal neuroendocrine tumors (30,31) and is consistent with results from the present study.

Preoperative evaluation of the depth of tumor invasion can minimize the residual edge of deep resection (32). Lugol iodine staining, NBI amplification and EUS can all be used to evaluate lesion size and depth of tumor invasion (33,34). Through the above methods, it is possible to reduce the residual margin in the process of endoscopic resection. Furthermore, unnecessary resection should be avoided to prevent esophageal stenosis.

The degree of tumor differentiation has also been previously established to be an independent risk factor (31,35-37). However, no similar reports exist regarding esophageal cancer. Poorly differentiated tumors are typically more likely to invade the vascular system and lymph nodes earlier or cause deep infiltration (38). In the present study, only 23 (7.5%) poorly differentiated lesions were diagnosed in 308 specimens with negative margins. By contrast, the proportion of positive margin specimens (21 poorly differentiated, representing 28.8% of 73 specimens) was significantly higher compared with that of negative margin specimens. In a previous study with gastric cancer, in the high-risk category, the benefit of surgery appears to be positive, since the cancer-specific survival rate in the salvage surgery group was higher compared that in the follow-up group (39). These data suggest that if biopsy indicates poorly differentiated tumors and if the patient's physical conditions allow, more aggressive treatment strategies should be recommended. Due to the limited follow-up time, no corresponding data were available and these patients require continuous close attention.

It remains unclear whether surgery and other medical interventions should be actively performed for patients with residual margins after endoscopic resection. For the designation of subsequent treatment plans, the patient's age, complications and willingness should also be considered. In this group of data, amongst the nine patients with positive deep margins, six patients received surgical treatment, two patients received radiotherapy and chemotherapy, whereas one patient was closely observed. No recurrence was found during the follow-up. Among the 64 patients with positive lateral margins, one patient received radiotherapy, one patient received chemotherapy, six patients received surgical treatment, 20 patients received additional EMR or ESD, eight patients were lost to follow-up and the remaining 28 patients were closely observed. During the follow-up period, five patients succumbed to cardiovascular and cerebrovascular diseases whereas no recurrence was found in other patients. In the present study, a preliminary prognostic analysis of patients with positive margins after endoscopic resection of early esophageal cancer was performed. A more detailed prognostic analysis needs to be verified by a multicenter study with a longer term of follow-up.

The present study has a number of limitations. The present study is only a retrospective single-center study, not a randomized controlled study. Only one pathologist participated in the analysis of the tissues. Therefore, there may be potential selection bias in the present study. Prospective clinical trials may be conducted in the future to further verify these results.

In conclusion, the present study analyzed the risk factors associated with the residual margin and the prognosis of patients. According to the results of data analysis, it is highly recommended to apply EUS for evaluating the depth of tumor invasion, determining the depth of lesion invasion and the indication of endoscopic resection before operation, all of which can effectively prevent a residual margin. If biopsy indicates a poorly differentiated tumor, more aggressive treatment strategies may be required to prevent recurrence after endoscopic resection.

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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 critically reviewed the manuscript, and read and approved the final manuscript.

Ethics approval and consent to participate

All patients and their families 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 (Shijiazhuang, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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