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Endoscopic submucosal dissection for superficial esophageal cancer with near-circumferential lesions: our experience with 40 patients

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Abstract
Background Nowadays, there are few reports indicating whether early esophageal cancers (EsC) with near-circumferential lesions are still appropriate for the endoscopic submucosal dissection (ESD) procedure.
Methods Between November 2009 and December 2013, a total of 40 patients with early esophageal cancers were treated with ESD. The characteristics of the patients, the ESD procedure variables, the rates of en bloc resection, and the major complications were evaluated. The outcomes listed were reliably followed up, and postoperative endoscopic balloon dilation was conducted to treat the esophageal strictures.
Results A total of 40 patients with superficial esophageal cancers were treated with ESD procedure. The extent of the lesions as a proportion of the whole circumference of the esophageal lumen ranged from three-quarters (18/40) to four-fifths (4/40) and complete circumference (18/40). The median longitudinal diameter of the lesions was 50 mm. The median procedure time was 92.5 min (range, 70–125 min). The en bloc resection rate was 100 % (40/40). Immediate bleeding, perforation, and postoperative stenosis were noted in 7.5 (3/40), 7.5 (3/40), and 45 % (18/40) of the patients. The median number of endoscopic balloon dilations (EBDs) was 4 (range 1–14). Additional surgical treatment was performed in 2 cases, and local recurrence was detected in 1 patient (2.5 %). 2 patients (5 %) died of EsC 3 months after ESD.
Conclusions These data will greatly expand the criteria for the use of ESD in esophageal cancer and increase the number of patients eligible for endoscopic treatment and the acceptance of the ESD procedure.

Keywords Endoscopic submucosal dissection · Esophageal cancer · Near-circumferential · Endoscopic balloon dilation (EBD)

Esophageal cancer (EsC) has become the eighth most commonly occurring cancer in the world because of its extremely aggressive nature and poor survival rate [1], which are characterized by several striking features: increasing incidence, male predominance, lack of preventive measures, lack of opportunities for early detection, demanding surgical therapy and care, and poor prognosis [2]. Currently, early detected EsC can be cured by esophagectomy, chemoradiotherapy, and endoscopic resection [3–5]. In comparison with the conventional treatment, more and more favorable outcomes have shown that endoscopic resection is an effective treatment for early EsC without metastasis.

Endoscopic submucosal dissection (ESD), a new endoluminal therapeutic technique involving the use of cutting devices that permit the en bloc resection of large lesions, was developed for stomach neoplasms and superficial esophageal cancers [6]. It is superior to conventional endoscopic mucosal resection (EMR) in terms of its en bloc resection rate and lower local recurrence rate [7, 8]. Although ESD is gaining increasing attention, it remains a challenging technique that is time-consuming and associated with a higher rate of complications, including

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perforation, massive bleeding, and post-procedural strictures [9, 10]. The incidence of these complications is greatly related to the lesion's size, the depth of invasion, and the excision extension of the lumen. For this purpose, the 2007 guidelines of the Japanese Esophageal Society for the diagnosis and treatment of esophageal cancer state that intraepithelial tumors (M1) and tumors invading the lamina propria (M2) that have spread to less than two-thirds of the circumference of the esophageal lumen are absolute indications for esophageal endoscopic resection [11]. Since strictures will develop particularly frequently when the resection involves more than 75 % of the circumference of the lumen [9], endoscopic resection is limited to lesions that do not exceed two-thirds of the circumference due to the chance of post-procedural strictures [11].

There are few reports indicating whether early EsC with near-circumferential lesions could still be applicable for the ESD procedure. Therefore, the aim of our study was to assess the feasibility and safety of the ESD procedure, as used for early EsC with near-circumferential lesions.

Patients and methods

Patients

This study included 40 consecutive patients who were treated with ESD at the endoscopic center of Xinqiao Hospital, Third Military Medical University (Chongqing, China) from November 2009 to December 2013. This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethical Committee of Xinqiao Hospital of Third Military Medical University (Chongqing, China).

All lesions were found during routine upper gastrointestinal endoscopy, and no prior treatment was given before ESD. The inclusion criteria were as follows: (1) histologically proven esophageal cancer or precancerous lesions; (2) lesion more than 75 % of the circumference or circumferential lesion; (3) mucosal cancer including in situ lesion; and (4) no lymph node or distant metastasis. Patients were excluded if they had (1) a lesion less than three-quarters of the circumference; (2) local lymph node metastasis; (3) severe cardiopulmonary diseases; or (4) non-correctable coagulopathy. Finally, a total of 40 patients (20 men, 20 women; mean age, 61.5 years; range, 42–79 years) with early esophageal cancer or precancerous lesions were selected as participants fulfilling the above criteria. Written informed consent was obtained from all patients before the operation. Information was collected and analyzed regarding lesion type, location, and size. The detailed clinicopathological features of the patients are summarized in Table 1.

Table 1 Clinical and histopathologic characteristics of the patients

Number of patients	40
Age, mean ± SD (range), years	61.5 ± 9.85 (42–79)
Gender	
Male	20 (50 %)[a]
Female	20 (50 %)[a]
Lesion location	
Upper	13 (32.5 %)[a]
Middle	14 (35 %)[a]
Lower	13 (32.5 %)[a]
Longitudinal diameter, mm	
Median	50
Range	20–170
Circumferential extent	
≥3/4	18 (45 %)[a]
≥4/5	4 (10 %)[a]
≥1	18 (45 %)[a]
Macroscopic type\	
IIa	11 (27.5 %)[a]
IIb	22 (55 %)[a]
IIc	4 (10 %)[a]
IIa + IIc	3 (7.5 %)[a]
Pathological type	
Squamous cell carcinoma	21 (52.5 %)[a]
Well differentiated	9 (42.8 %)[a]
Moderately differentiated	6 (28.6 %)[a]
Poorly differentiated	6 (28.6 %)[a]
High-grade intraepithelial neoplasia	18 (45 %)[a]
Low-grade intraepithelial neoplasia	1 (2.5 %)[a]
Depth of invasion	21
M1	4 (10 %)[a]
M2	4 (10 %)[a]
M3	8 (20 %)[a]
SM1	3 (7.5 %)[a]
SM2	2 (5 %)[a]
Symptoms	
Asymptomatic	23 (57.5 %)[a]
Dysphagia	10 (25 %)[a]
Thoracodynia	2 (5 %)[a]
Obstruction	4 (10 %)[a]
Dysphagia and thoracodynia	1 (2.5 %)[a]
Concomitant disease	
None	38 (95 %)[a]
Hypertension	1 (2.5 %)[a]
Diabetes and hypertension	1 (2.5 %)[a]

SD standard deviation, *mm* millimeter, *SM1* slight submucosal invasion, less than 500 μm, *SM2* deeper submucosal invasion, 500 μm or greater, *M2* intramucosal invasive carcinoma limited to the lamina propria mucosae, *M1* limited to the epithelium

[a] *n* (100 %)

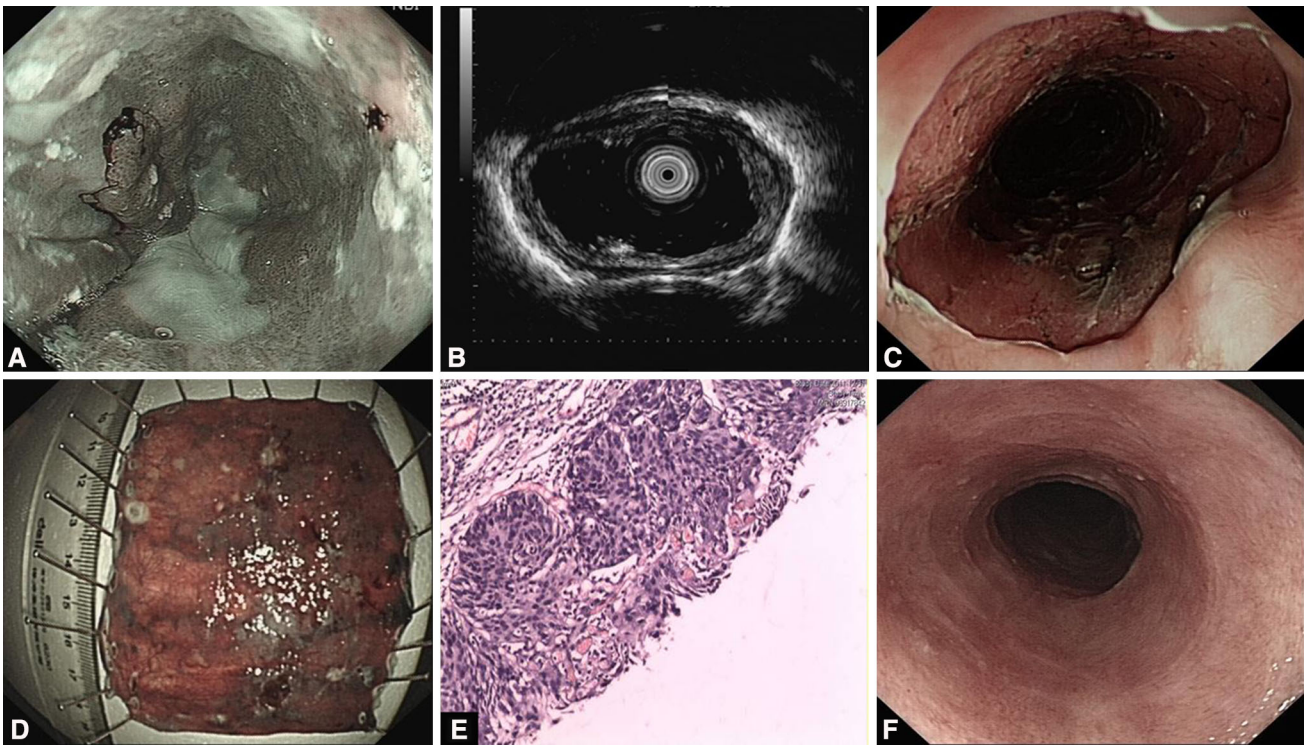

Fig. 1 Complete circular endoscopic submucosal dissection (ESD) for early superficial esophageal cancer without postoperative stricture **a** submucosal tumor was noted on NBI; **b** the same tumor observed using EUS; **c** artificial ulcer after the removal of the lesion; **d** resected en bloc specimen; **e** histological evaluation of the resected specimen; and **f** complete healing with no stricture or recurrence after 6 months

ESD procedure

An endoscope with a water jet system (GIF-Q260J, Olympus, Tokyo, Japan) was used for the ESD procedure with a transparent cap attached to its tip. A needle knife (NM-400U-0423, Olympus), a hook knife (KD-620 LR, Olympus), an insulated-tip knife-2 (KD-611 L, Olympus), and a hemostatic forceps (FD-410 LR, Olympus) were used during the procedure. VIO200D and APC-ICC200 (ERBE ELEKTROMEDIZIN GMBH, Germany) were set to the forced coagulation mode (effect 2, output 40 W) to incise the mucosal layer.

Standard steps were performed as follows (Fig. 1): The lesions were detected with white light endoscopy and magnifying narrow-band imaging (NBI) to estimate their depth and extent of invasion. Then, iodine staining was performed using 2 % Lugol's solution to further determine the extent of the lesion. A circumferential mark was made at least 5 mm outside the tumor margin using an argon knife. The solution used for the submucosal injection was combined with 40 ml glycerin fructose, 2.5 ml sodium hyaluronate, and 0.5 ml methylene blue and was then injected into the submucosal layer to elevate the lesion. The mucosa was incised around the markings with a hook knife in the Endocut mode (Effect 4, Duration 2, Interval 3). Further, the submucosal dissection was performed with a hook knife or IT-2 knife. To control bleeding during the ESD procedure, hemostatic forceps were used in the soft coagulation mode (Effect 5, 60 W). Each patient was sedated with an intravenous injection of 7.5 mg diazepam and 50 mg pethidine, and additional diazepam (2.5 mg) or pethidine (25 mg) was given alternately as needed for conscious sedation throughout the ESD. Procedure-related bleeding after the ESD was defined as bleeding that required transfusion or surgical intervention or bleeding that caused the hemoglobin level to drop by 2 g/dL [12]. ESD-related perforation was diagnosed endoscopically or by the presence of free air on a chest X-ray or CT, and a hemoclip was applied. Insufflation with carbon dioxide (CO_2) was performed if necessary. Resected specimens were retrieved, completing the procedure. The procedure time was defined as the time from the commencement of the markings around the lesion to the end of the prophylactic hemostasis of the resected area. The procedure time, histological data (en bloc or piecemeal resection, *R*0 laterally and in depth), and data on complications during and after the procedure were recorded. All endoscopic procedures were performed by the same expert endoscopist.

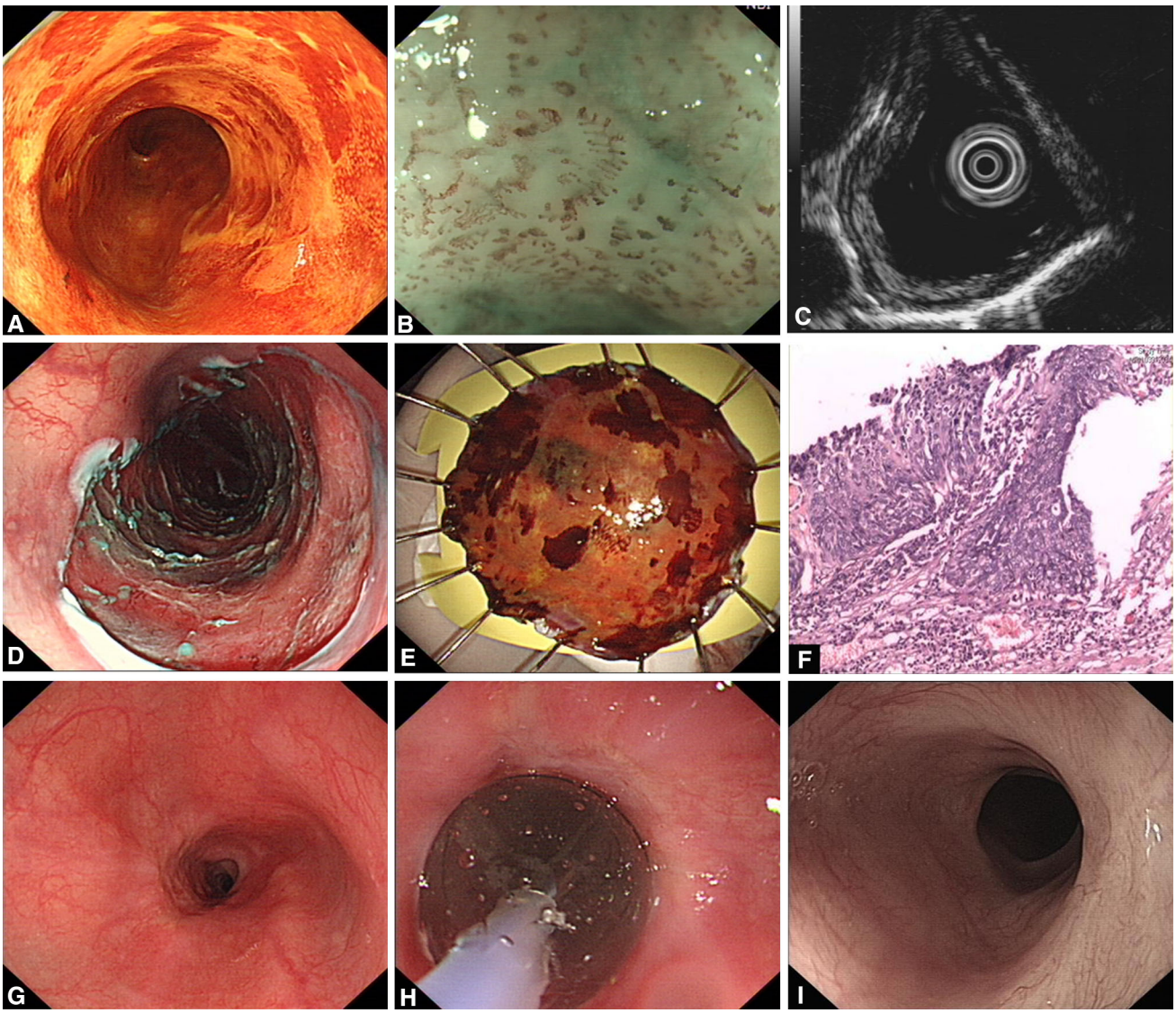

Fig. 2 Endoscopic submucosal dissection of superficial esophageal cancer and endoscopic balloon dilation (EBD) in patients with esophageal strictures after ESD **a** detection of the lesion (unstained part) using chromoendoscopy with iodine staining; **b** the lesion observed using narrow-band imaging (NBI); **c** the same tumor observed using EUS; **d** artificial ulcer after the removal of the lesion; **e**: resected *en bloc* specimen; **f** histological evaluation of the resected specimen; **g** severe stricture that arose after ESD; **h** balloon dilation for the stricture; **i** the appearance of the esophagus after EBD

Histopathologic and therapeutic evaluation

The longitudinal diameter of the resected specimens that were stretched appropriately was measured from the oral edge to the anal edge (Figs. 1, 2). The tumors' longitudinal diameters were also documented. Then, the specimens were fixed in formalin, paraffin-embedded, cut into 2 mm-wide strips perpendicular to the lesion base, and evaluated by histopathologic examination. Two pathologists examined the specimens to determine their histopathologic diagnosis. The macroscopic types and depth of invasion were classified according to the Paris endoscopic classification of superficial neoplastic lesions [13].

To assess the therapeutic efficacy of the endoscopic submucosal dissection, the rates of en bloc and complete resection, size of resected specimens, procedure times, and rates of major complications were recorded and evaluated. En bloc resections are resections completed in one piece [14]. Complete resection was defined as an en bloc resection with histologically confirmed tumor-free margins. On the other hand, incomplete resection was defined as tumor-positive margins. Endoscopically resected lesions with margins that could not be evaluated histopathologically because of electrosurgical or mechanical damage were also classified as incomplete resections [8].

Postoperative management and follow-up

Patients were permitted to drink a small amount of water 3 h after the ESD procedure, and a light meal was permitted the next day in the absence of severe complications. A proton pump inhibitor and sucralfate are given until healing of the post-procedure ulcers has been confirmed. Oral prednisolone was administered to these patients, starting at a dose of 30 mg daily on the third post-ESD day and tapering gradually (daily 30, 30, 25, 25, 20, 15 10, 5 mg for 7 days each) until finally stopped 8 weeks later [19].

Patients underwent intensive follow-up in our hospital. The patients were followed up with conventional white light endoscopy, EUS, NBI, iodine staining and contrast-enhanced CT scheduled at 1, 3, 6 and 12 months after the last ESD procedure and then annually thereafter until the patients' death. During follow-up, endoscopic balloon dilation (EBD) using a CRE balloon (Boston Scientific Co., Boston, USA) was performed if postoperative strictures occurred (Fig. 2). The size of the balloon was chosen according to the degree of esophageal strictures, and the EBD durations depended on each individual patient's symptoms until his or her dysphagia was resolved. The biopsy specimens taken during each follow-up endoscopy were sampled from any mucosal abnormalities to assess the risk of local recurrence. Local recurrence was diagnosed when a carcinomatous area was detected adjacent to an ESD scar and could be verified histologically. If a recurrence was identified, additional chemotherapy or surgery was then recommended.

Statistical analysis

SPSS statistical software (SPSS Inc.16.0.2, Chicago, Illinois, USA) was used for data analysis (CIA Version 2.2.0, London, UK). Mean and standard deviation (SD) were used to describe normally distributed values and the median of values with skewed distributions.

Results

Patients and clinicopathologic features

A total of 40 patients (20 male, 20 female; mean age 61.5 years, range 42–79) were enrolled, and 40 lesions were treated with the ESD procedure. Patient and tumor characteristics were summarized in Table 1. The lesions were detected in the upper esophagus in 13 cases, in the middle esophagus in 14 cases, and in the lower thoracic esophagus in 13 cases. The overall median longitudinal diameter of the lesions was 50 mm (range 20–170). The circumferential extent of the lesions was classified as the entire circumference (that is, circumferential extent 100 %) in 18 cases. Out of all 40 lesions, 21 (52.5 %) were carcinoma, 18 were high-grade intraepithelial neoplasia (HGIN), and 1 was low-grade intraepithelial neoplasia. Regarding the macroscopic types, 14 lesions were type IIa, 22 were type IIb, and 4 were type IIc according to the Paris endoscopic classification [13???]. Out of the 10 patients who had dysphagia, 2 had thoracodynia, 4 had obstructions, and the remaining patients were asymptomatic. The comorbidities included hypertension and diabetes mellitus in 2 patients. Each of these concomitant situations was carefully assessed and treated with ESD under an anesthetist's supervision.

Table 2 Treatment outcomes of endoscopic submucosal dissections

Specimen size (mm)	
Median	80
Range	(40–200)
Complete resection	40 (100 %)[a]
En bloc resection	40 (100 %)[a]
Tumor-free margin *R*0 resection	40 (100 %)[a]
Operation time (min)	
Median	92.5
Range	70–125
Adverse events	
Immediate bleeding	3 (7.5 %)[a]
Perforation	3 (7.5 %)[a]
Stenosis	18 (45 %)[a]

*R*0, tumor-free horizontal and vertical margins

[a] *n* (100 %)

Treatment outcomes of ESD

The main treatment outcomes are summarized in Table 2. The overall median longitudinal length of the resected specimens was 80 mm (range 40–200). En bloc resection was achieved in all lesions. Complete resection was defined as an en bloc resection with histologically confirmed tumor-free margins. Overall, the complete resection rate was 100 % (40/40), with a 100 % *R*0 (tumor-free horizontal and vertical margins) rate. The median duration of the ESD procedure was 92.5 min (range, 70–125 min).

No severe complications or death-related events were observed in the 40 patients undergoing ESD. Table 2 shows the complications that occurred during the ESD procedure. Immediate bleeding occurred in 3 patients during the ESD, and hemostasis was successful after electrocoagulation and the application of the hemostatic clip. Perforations occurred in 3 patients, and all responded immediately to conservative medical treatment. Esophageal strictures occurred in 18 patients after ESD.

Table 3 Clinical outcomes of 40 patients who underwent ESD

Duration of follow-up (months)	
Median	14
Range	6–55
Alive without recurrence	36 (90 %)[a]
Alive with local recurrence	1 (2.5 %)[a]
Died of other reasons	3 (5 %)[a]

[a] *n* (100 %)

Table 4 Outcomes of EBD and further treatments of those patients undergoing EBD

Patients undergoing EBD	18
Main symptom	
Asymptomatic	8
Dysphagia	9
Thoracodynia	1
Number of dilations	
Median	4
Range	1–14
Technical success	18/18 (100 %)[a]
Clinical success	16/18 (88.9 %)[a]
Further treatment	
Chemotherapy	1
Surgery	2

Technical success was defined as a successful dilation without major adverse events, such as perforations or massive bleeding. Clinical success was defined as an improvement in the clinical symptoms. EBD, endoscopic balloon dilatation

[a] *n* (100 %)

Clinical outcomes and follow-up

The median follow-up period was 14 months (range 6–55). In the 40 patients with ESD, local recurrence was found in only 1 patient with M3 cancer during the period of follow-up, and further chemotherapy was administered to this patient. Two patients developed lung metastasis and died of the disease 3 months after ESD; 1 patient committed suicide and was lost to follow-up (Table 3). The rest of 37 patients were absolutely adherence to the follow-up.

Additional treatment

During the follow-up, certain additional treatments were undertaken for those patients who underwent the ESD procedure (Table 4). Among the 18 patients who suffered from esophageal strictures, 9 patients had dysphagia, 1 had thoracodynia, and the rest were asymptomatic. All patients with post-strictures were treated by endoscopic balloon dilation (EBD) a median of 4 times (range 1–14 times). Balloon dilation was repeated until the endoscope could smoothly pass through the lumen, and no adverse events related to EBD were observed in any patients (Fig. 2). Technical success was achieved in all patients. The treatment success rate was 88.9 % (16/18), but 2 patients experienced recurrent dysphagia and no relieved symptoms until the end of follow-up. Therefore, additional surgical treatment was pursued for those 2 patients who experienced no relief of symptoms after several EBD procedures. A local recurrence was observed in 1 patient, and further chemotherapy was recommended.

Discussion

The incidence of EsC has increased sharply over the past few decades, and early diagnosis and treatment are essential to improve the survival rate of EsC. In recent years, with the development of endoscopy, the early detection rate of EsC has been greatly increased. Originally, once diagnosed, EsC was always recommended for surgical radical resection due to concern over the risk of metastasis. However, such a major surgery carries the risk of over-treatment and diminishes postoperative life quality [15]. Currently, endoscopy has gradually been developed into an important treatment regimen for early EsC because of its relative lack of trauma compared to surgery.

ESD is a useful technique that is aimed at resecting early tumors in the gastrointestinal tract without compromising the integrity of the wall, allowing for en bloc resection and the proper pathological evaluation of specimens [16]. With the development of endoscopic techniques, ESD may also be used for relatively large superficial esophageal epithelial cancers. Despite the inspiring characteristics of this treatment, ESD is still limited to only those cancer lesions indicated by the guidelines. Currently, the 2007 guidelines of the Japanese Esophageal Society for the diagnosis and treatment of EsC state that early EsC that has spread to more than two-thirds the circumference is a relative indication [11]. However, the Chinese consensus of endoscopic experts for ESD treatment emphasizes only the early EsC and depth of invasion, without considering lesion size. Moreover, there is very little research that has reported whether early EsC with lesion size more than two-thirds circumference or complete circumference could still be applicable for ESD. We believe that these early EsC that have spread to more than two-thirds of the circumference of the lumen can be resected using ESD regardless of lesion location or size as long as no lymphatic or blood vessel invasion has occurred. These provisions represent a useful complement for the existing guidelines.

In this present study, we applied ESD in 40 early EsCs with near-circumferential lesions. All of the esophageal

lesions were larger than three-quarters of the circumferential extent of the lumen, and 21 lesions were histologically confirmed squamous cell carcinoma after ESD procedures. For submucosal cancer or other undifferentiated cancer, some guidelines do not advise endoscopic treatment because of the high rates of metastasis and recurrence. In our study, all lesions were removed en bloc with histologically confirmed tumor-free margins, and the resected area was expanded appropriately to ensure negative margins. None of the lesions confined to the mucosal layers presented with metastasis, and regarding mucosal and submucosal cancers, only 1 patient who did not undergo additional surgery because of advanced age developed distant metastasis. Therefore, for those patients who have a poor status or refuse surgical treatment, ESD could be an appropriate alternative, even if the complication rate increased with tumor size and depth of invasion.

The complications observed in this study included bleeding, perforations, and stenosis. Obviously, the perforation rate will increase if the tumor size is too large. As shown in our data, the circumferential extent of all the included lesions exceeds three-quarters. Only three perforations occurred during the ESD procedure in this series, and all responded immediately to the conservative medical treatment. Immediate minor bleeding was relatively small and could be successfully managed or reduced by coagulation or proton pump inhibitors. The absence of delayed bleeding and lower rate of complications may be explained by the high level of expertise attained by the endoscopists involved in this study.

Currently, ESD remains a challenging and time-consuming technique. However, when the risk of residual tumors and recurrence is considered, the procedural time required for ESD is not a great problem. We evaluated the relationship between the procedure time and the clinicopathological factors of the patients. The tumor's longitudinal diameter and the circumference of the esophagus were positively associated with the length of the procedure time. Nevertheless, lesion location, macroscopic type, and depth of invasion were not associated with the duration of procedure time. Complete resection is especially important because local recurrence will arise from the small remnants of cancer left on the margins of a resection [17]. In the current study, the ESD procedure was effective, with high en bloc and complete resection rates (100 %). Recurrence occurred in only 1 patient (2.5 %, 1/40) who had an M3 invasion and a poor general condition due to older age and concomitant diseases. Therefore, ESD can greatly decrease the risk of local recurrence because of its en bloc removal of cancerous lesions.

As we know, postoperative strictures have become a major concern for long-term outcome after the ESD procedure. In a previous study, multivariate analysis revealed that a circumferential extent greater than three-quarters and a histological depth of M2 were reliable independent predictors for postoperative strictures [18]. We also found that the circumferential extension and depth of invasion were positively associated with the occurrence of esophageal stenosis. The incidence rate of post-ESD strictures in this study was 45 % (18/40), significantly lower than that in the previously reported research. Considering the lower rate of strictures, we believe that oral prednisolone after ESD may be a key factor because oral prednisolone has been reported to greatly decrease the rate of strictures and EBD sessions [19]. Furthermore, endoscopists would be able to retain the submucosa as much as possible during the procedure, potentially decreasing the rate of strictures after ESD. Last but not least, the experience and operative skills of the endoscopist are also important in decreasing the rate of strictures.

Currently, several management strategies exist for strictures after esophageal ESD. EBD is considered to be an effective treatment for post-ESD strictures; the present study showed technical and clinical success rates at least 3 months after balloon dilation of 100 and 88.9 %, respectively (Fig. 2). However, we believe that this period may be too short to properly represent the outcomes, and longer follow-ups should be conducted. However, these success rates still produced encouraging results and indicated the long-term efficacy of balloon dilation for post-ESD strictures. Additionally, esophageal stent is a safe and effective method of preventing esophageal strictures in cases where a 75 % circumference of the esophagus has been resected after ESD [20]. Steroid gel application is another effective means for preventing esophageal strictures after ESD [21]. Recently, esophageal strictures have been managed using new technologies, such as biodegradable stents or autologous oral mucosal sheets. Before these methods are used in clinical applications, our experience with EBD for complete near-circumferential ESD may offer an alternative to decrease the risk of esophageal strictures. Therefore, esophageal strictures after an ESD procedure represent no great obstacle against conducting ESD in EsC with relatively large circumferential lesions.

There are several limitations in the present study. The first is that the sample size is small, and the study was conducted at a single institution. The second limitation is that a number of patients were observed for less than 1 year; the periods of follow-up were thus significantly different. Data from a well designed, randomized, and multicenter prospective study using standardized criteria is desirable. Nevertheless, the results of this present study may provide a useful foundation for future studies.

In conclusion, the present study demonstrates that ESD may be a useful and safe treatment with a high success rate for early EsC with near-circumferential lesions. ESD may

greatly decrease the risk of local recurrence because of its en bloc removal of cancerous lesions. Based on the existing guidelines of the Japanese Esophageal Society, we found that submucosal cancer (SM1 and SM2) that spreads to more than two-thirds of the circumference could still be effectively removed by applying the ESD technique, greatly expanding the criteria for ESD for EsC. These expanded criteria will increase the number of patients eligible for endoscopic treatment and contribute to the acceptance of ESD procedures. Long-term follow-up and further studies are needed to confirm or extend our findings.

Disclosures Bo Tang, Jian-Ying Bai, Xiao-Yan Zhao, Chao-Qiang Fan, Xin Yang, Lei Deng, Shi-Ming Yang, and Jing Yu have no conflicts of interest or financial ties to disclose.

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