**Name of Journal:** ***World Journal of*** ***Gastroenterology***

**Manuscript NO: 38556**

**Manuscript Type:** **ORIGINAL ARTICLE**

***Retrospective Study***

**Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal squamous cell carcinoma and precancerous lesions**

Wang J *et al*. ESTD for early esophageal cancer

Jin Wang, Xiao-Nan Zhu, Lin-Lin Zhu, Wei Chen, Yi-Han Ma, Tao Gan, Jin-Lin Yang

**Jin Wang, Xiao-Nan Zhu, Wei Chen, Yi-Han Ma, Tao Gan, Jin-Lin Yang,** Department of Gastroenterology and Hepatology, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China

**Jin Wang,** State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, Chengdu 610041, Sichuan Province, China

**Lin-Lin Zhu,** Department of General Practice, West China Hospital of Sichuan University, Chengdu, 610041, Sichuan Province, China

**ORCID number:** Jin Wang (0000-0003-0944-0793); Xiao-Nan Zhu (0000-0001-5979-2143); Lin-Lin Zhu (0000-0002-4740-2838); Wei Chen (0000-0003-1905-8408); Yi-Han Ma (0000-0003-4605-0217); Tao Gan (0000-0002-7331-062X); Jin-Lin Yang (0000-0001-8726-7258).

**Author contributions:** Wang J, Zhu LL, Gan T and Yang JL designed the research; Wang J, Zhu XN, Zhu LL, Chen W and Ma YH performed the research; Wang J, Zhu XN, Chen W and Ma YH collected the data; Wang J, Zhu LL, and Gan T analyzed the data; Wang J, Zhu LL, and Yang JL wrote the paper.

**Supported by** theScience and Technology Department of Sichuan Province for Scientific Research, No. 2015SZ0123.

**Institutional review board statement:** This study was reviewed and approved by Institutional Review Board of the West China Hospital of Sichuan University.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** We have no financial relationships to disclose.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Correspondence to:** **Jin-Lin Yang, MD, PhD, Chief Doctor, Doctor, MHSc, Professor,** Department of Gastroenterology and Hepatology, West China Hospital of Sichuan University, 37th Guoxue Alley, Chengdu 610041, Sichuan Province, China. [mouse-577@163.com](mailto:mouse-577@163.com)

**Telephone:** +86-28-85423326

**Fax:** +86-28-85423326

**Received:** March 16, 2018

**Peer-review started:** March 17, 2018

**First decision:** April 18, 2018

**Revised:** May 2, 2018

**Accepted:** June 9, 2018

**Article in press:**

**Published online:**

**Abstract**

***AIM***

The aim of this study was to evaluate the clinical outcomes of patients who underwent endoscopic submucosal tunnel dissection (ESTD) for esophageal squamous cell carcinoma (ESCC) and precancerous lesions.

***METHODS***

ESTD was performed in 289 patients. The clinical outcomes of the patients and pathological features of the lesions were retrospectively reviewed.

***RESULTS***

A total of 311 lesions were included in the analysis. The en bloc rate, complete resection rate and curative resection rate were 99.04%, 81.28% and 78.46%, respectively. The ESTD procedure time was 102.4±35.1 min, the mean hospitalization time was 10.3 ± 2.8 d and the average expenditure was 3766.5 ± 846.5 dollars. The intraoperative bleeding rate was 6.43%, the postoperative bleeding rate was 1.61%, the perforation rate was 1.93%, and the postoperative infection rate was 9.65%. Esophageal stricture and positive margin were severe adverse events with an incidence rate of 14.79% and 15.76%, respectively. No tumor recurrence occurred during the follow-up period.

***CONCLUSION***

ESTD for ESCC and precancerous lesions is feasible and relatively safety, but for large mucosal lesions, the rate of esophageal stricture and positive margin is high.

**Key words:** Superficial esophageal squamous cell carcinoma; Endoscopic submucosal tunnel dissection; Efficiency; Safety; Esophageal stricture

**© The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Endoscopic submucosal tunnel dissection (ESTD) is a modified technique based on endoscopic submucosal dissection. In this paper, we found ESTD is feasible and relatively safety for treating esophageal squamous cell carcinoma (ESCC) and precancerous lesions, in which the en bloc rate is high, while the adverse event rate is relatively low. But when treating large mucosal lesions, ESTD has a high rate of esophageal stricture and positive margin, which need further treatment. Furthermore, we found the pathology of preoperative biopsies upgraded after ESTD, which remind us the accuracy of biopsy to diagnosis ESCC should be reconsidered.

Wang J, Zhu XN, Zhu LL, Chen W, Ma YH, Gan T, Yang JL. Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal squamous cell carcinoma and precancerous lesions. *World J Gastroenterol* 2018; In press

**INTRODUCTION**

Endoscopic submucosal dissection (ESD) is becoming the standard treatment for early gastrointestinal cancers, as it has a higher en bloc resection rate and a lower recurrence rate than endoscopic mucosal resection (EMR)[1,2], while it can be used to resect lesions with a diameter greater than 2 cm[3]. However, esophageal ESD faces many difficulties because of the narrow esophageal lumen and thin walls[4-6]. When using conventional ESD treatment for large mucosal lesions, and especially for lesions with a circumference that exceeds three fourths of the esophageal lumen, multiple submucosal injections are required, which could prolong the procedure time and thereby increase the risk of complications[5]. Even worse, with the resected mucosa blocked in the lumen, the endoscopic view becomes unclear and may increase the difficulty of complete resection[6]. To overcome these difficulties, some modified ESD techniques have been introduced, such as ling traction method[6], clip traction method[7], and the thread-traction method[8]; however, none of these methods was suitable for extensive application.

In 2009, Linghu *et al*[9] used a “submucosal tunnel” to successfully resect a circumferential esophageal mucosal lesion, which was termed as endoscopic submucosal tunnel dissection (ESTD) afterwards[5]. Compared with conventional ESD, ESTD has many technical advantages, as it resects the mucosal lesions by creating a submucosal tunnel between the mucosal layer and muscular layer, after which therapeutic endoscopy can enter the tunnel and acquire a clear operative view. Moreover, the CO2 injected in the operation can help the blunt dissection of the mucosal layer, thereby reducing the number of submucosal injections, shortening the procedure time, increasing the resection speed, and reducing the injury of the muscular layer[10-12]. This approach can also incise the submucosa more completely, thereby reducing the risk of tumor metastasis and recurrence, as shown in our previous study[13]. However, there are no studies that have verified the feasibility of ESTD in superficial esophageal squamous cell carcinoma (ESCC) and precancerous lesions in a large sample. The aim of this study was to assess the efficacy and safety of ESTD in treating superficial ESCC and precancerous lesions in a relatively large sample.

**MATERIALS AND METHODS**

***Patients and endoscopic characteristics***

A prospectively collected endoscopic therapy database was analyzed retrospectively. All of the patients with superficial ESCC and precancerous lesions who underwent ESTD in the Digestive Endoscopy Center of West China Hospital from March 1, 2013 to May 1, 2017 were enrolled. A total of 355 patients with superficial esophageal cancer underwent endoscopic treatment. We excluded patients with esophageal adenocarcinoma, EMR/ESD procedure, and incomplete clinical data. Finally, 289 patients with 311 lesions were analyzed (Figure 1). All of the lesions were confirmed by pathological evaluation from biopsy specimens according to Japanese classification of ESCC[14] before ESTD procedure. The clinical records and ESTD records were collected, and demographic and endoscopic characteristics were retrospectively reviewed. The endoscopic type of the lesions was assessed according to the Paris endoscopic classification[15]. This study was approved by the Ethics Committee of the West China Hospital of Sichuan University.

***ESTD procedure***

Before ESTD, all of the lesions were evaluated by endoscopy, EUS, and CT of chest and abdomen. Prophylactic antibiotics were used in patients with large mucosal lesions (circumference ≥ 3/4) at half an hour before ESTD. ESTDs were performed by one endoscopist with an experience of more than 200 cases of ESD procedure. ESTD procedure includes 6 steps, as shown in Figure 2. When the lesion was detected by white light endoscopy, it was carefully observed under narrow band imaging (NBI) and iodine staining. Next, the margins were marked by a dual knife (KD-650Q, Olympus, Tokyo, Japan). A liquid mixture of 1:10000 adrenaline saline, sodium hyaluronate, glycerin fructose and indigo carmine was used in submucosal injection. Both anal-side and oral-side incisions were made after submucosal injection, after which the submucosal tunnel was established from the oral side to the anal side and stopped at the anal-side incision. Thereafter, the remaining lateral margin incisions were made; thus, the lesion was completely resected. Finally, wound hemostasis was carefully performed by hemostatic forceps (FD-410LR, Olympus) or argon plasma coagulator (ERBE Corporation).

***Postoperative strategies and follow-up***

Patients were allowed to orally feed from the third day after ESTD, while treatment with proton pump inhibitors, hemostatics and nutritional supports was initiated. The vital signs were monitored and gas-related complications were closely detected, including subcutaneous emphysema, mediastinal emphysema, and pneumoperitoneum. All patients were asked to join in the follow-up plan, and surveillance endoscopy with iodine staining was performed at 1, 3, 6, 12, 24 and 36 mo after ESTD. Biopsies for suspicious lesions were also recommended. The patients with non-curative resection underwent either additional treatment (re-ESD, radiotherapy, surgery) or close surveillance.

***Outcome measures***

The primary outcomes included en bloc resection rate, complete resection rate and curative resection rate, as well as the data acquired from ESTD procedure, such as procedure time, dissection speed, and the specimen area. The secondary outcomes were the rates of adverse events, including intraoperative and postoperative bleeding, perforation, muscular injury, postoperative infection, esophageal stricture, positive margin, and local tumor reoccurrence. The symptom score of esophageal stricture was assessed according to Stooler’s dysphagia score[16].

***Definitions***

Procedure time was defined as the time from lesion marking to the termination of therapeutic endoscopy. Specimen area was calculated by the formula: S = (a + b/2) × (c + d/2), (a and b represent the maximum and minimum values of the length diameter, respectively, while c and d represent the maximum and minimum values of the width diameter, respectively). En bloc resection was defined as resection of the lesion by an entire specimen, while complete resection/R0 resection was defined as an en bloc resection with neoplasia-free margins (both horizontal and vertical margins). Curative resection was pathologically defined as a complete resection with a differentiated carcinoma with < 200 μm submucosal invasion and no lympho-vascular invasion.

Intraoperative bleeding was defined as blood volume > 50 mL and bleeding that could be effectively stopped in ESTD procedure. Postoperative bleeding was defined as the symptoms of hematemesis or/and melena, with hemoglobin levels being decreased by more than 20 g/L within 30 d after ESTD procedure[17]. Perforation was defined as a visible hole in esophageal wall, or the presence of subcutaneous emphysema, pneumothorax, mediastinal emphysema or pneumoperitoneum.

Esophageal stricture was defined when the standard GIF-Q260J (OLYMPUS) gastroscopy could not pass through the esophageal lumen and if the patient had dysphagia[18]. A positive margin was defined as the presence of a neoplastic cell in the horizontal or vertical margins. Residual tumor was defined as the presence of new tumor lesions in the primary resection site and its surrounding 1 cm area within 6 mo after ESTD. Tumor reoccurrence was defined as the presence of new tumor lesions in the primary resection site and its surrounding 1 cm area over 6 mo after ESTD procedure.

***Statistical analyses***

Continuous variables are represented by (average ± SD) and were compared by Student’s *t*-test. Categorical variables are represented by the rate and evaluated by Pearson chi square test or Fisher exact test. To analyze the risk factors of ESTD-associated complications, univariate and multivariate logistic regression analyses were performed (SPSS version 24.0, SPSS Inc, Chicago). *P*-value < 0.05 indicated statistical significance.

**RESULTS**

***Baseline characteristics of patients***

A total of 355 superficial esophageal patients underwent endoscopic treatments from March 1, 2013 to May 1, 2017, of which 66 patients were excluded for the following reasons: (1) Adenocarcinoma (*n* = 15); (2) EMR procedure (*n* = 10) or ESD procedure (*n* = 27); (3) incomplete lesion data (*n* = 6); and (4) lost to follow-up (*n* = 8), as shown in Figure 1. The demographic data are shown in Table 1. The average age of the patients was 61.39 ± 8.07 years with a male/female ratio of 2.17 (213/98). The lesions were mainly located in the middle third of the esophagus (64.31%). Thirty-one circumferential lesions were included in the final analysis (Table 1). The most common preoperative histological type was HGIN, as shown in Table 2.

***Treatment outcomes and complications***

Three hundred eleven lesions were successfully resected from 289 patients. The average specimen area was 14.1 ± 3.6 cm2, the mean procedure time was 102.4 ± 35.3 min, and the mean dissection speed was 18.6 ± 2.1 mm2/min. A total of 308 (308/311) lesions were resected by en bloc (99.04%), of which 49 were diagnosed with horizontal or vertical margin involvement by pathological evaluation; thus, the R0 resection rate was 81.28% (259/311). Twelve patients were diagnosed with lympho-vascular invasion (3.86%), of which 5 were combined with positive margin. We evaluated the invasion depth under microscopy and observed that 7 lesions had a submucosal invasion deeper than 200 μm. As a result, the curative resection rate was 78.46% (244/311). After post-ESTD pathological evaluation, 3 patients were diagnosed with residual cancer in horizontal margin and 12 in vertical margin, of which 5 patients had vascular invasion. Another 7 patients simply showed vascular invasion. All of the 22 patients were recommended an additional surgery. Finally, 17 patients underwent surgery, while the other 5 refused and were closely observed. The mean hospitalization day was 10.3 ± 2.8 d, while the average hospitalization expense was 3766.5 ± 846.5 dollars (Table 3).

After ESTD procedure, 30 patients had postoperative infection, of which 29 were pulmonary infection, and 1 was urinary-tract infection. All of the infections were cured by intravenous infusion of antibiotics. Moreover, 20 (6.43%) patients had intra-operative bleeding, and 5 patients had postoperative bleeding. All of these patients underwent endoscopic hemostasis, and no severe complications with regard to bleeding were observed. Six patients had esophageal perforation and were cured by conservative treatment. Forty-six patients had postoperative esophageal stricture, of which 36 (78.26%) underwent an average of 4.1 (2-19 times) endoscopic balloon dilation in a mean follow-up time of 20.2 mo. In addition, the dysphagia was almost relieved (Table 4), while the other 10 patients had obstinate stenosis were further managed by receiving endoscopic balloon dilatation every two weeks till dysphagia relieved.

***Pathology analysis***

We analyzed the pathological change between pre-ESTD biopsies and post-ESTD specimens and observed that HGIN accounted for 51.13% (159/311) of pre-ESTD biopsies, while in post-ESTD pathology, superficial invasive carcinoma accounted for 44.70% (139/311). The pre-ESTD and post-ESTD coincidence rate was 30.23% (94/311). Also, 50.21% (117/233) of HGIN and M1 lesions had a pathological upgrade after ESTD to superficial invasive carcinoma.

**DISCUSSION**

This study evaluated the efficacy and complications of ESTD in 289 patients with 311 esophageal mucosal lesions. ESTD is a new technique developed from ESD and tunnel endoscopy. There are currently few studies that have reported the efficacy and complications of ESTD in large samples. Gan *et a*l[13] reported endoscopic submucosal multi-tunnel dissection (ESMTD) for 7 circumferential lesions, in which all patients achieved R0 resection but suffered from esophageal stricture. Huang *et al*[10] compared the efficacy and complications rate between ESD and ESTD using a propensity score matching analysis and observed that ESTD can improve procedure efficacy and reduce injury to muscular layer due to a better view, more efficient vessel coagulation, and longer lasting submucosal liquid cushion. In our previous ESD procedure, we observed that the dissected mucosa shrank and blocked the lumen, making it difficult to obtain a clear view. While ESTD can avoid this obstacle by creating a submucosal tunnel, when therapeutic endoscopy enters the submucosal tunnel, it will acquire a clear operative view to facilitate observation of the submucosal vessels and muscular layer, thereby reducing the bleeding and perforation rate. For this reason, it is especially appropriate for large mucosal lesions[11]. Zhai *et al*[19] obtained similar findings and noted that ESTD is indicated when (1) lesions do not invade deeper than sm1 and have no evidence of lymph node metastasis and (2) the lesion’s circumference level ≥ 1/3 or the diameter ≥ 2 cm.

The reported en bloc and R0 resection rates of ESTD were 97.8% (92%-100%) and 85.6%（81.8%-100%）, which are similar to our study outcomes. However, our curative resection rate was 78.46% (244/311), mainly because we included large mucosal lesions. Also, 44.05% (137/311) of our lesions had a circumference level > 1/2, which may increase the risk of incomplete resection. Patients’ mean hospitalization stay was 10.3 ± 2.8 d, which is closely related to less hospitalization expenses (3766.5 ± 846.5) dollars compared with surgical treatment.

We evaluated the post-ESTD specimens’ pathological features and observed that 50.21% (117/233) of HGIN and M1 lesions upgraded to superficial invasive carcinoma after ESTD. Several reasons might contribute to this: First, the heavier the lesion is and the wider its range, the poorer the representativeness of the pre-ESTD biopsy. In large or multifocal lesions, even if multiple biopsies are taken, it is difficult to represent the whole picture of the lesion. Moreover, the esophagus wall is thin; thus, thus too deeply drawn or frequent biopsies will lead to bleeding, perforation and other biopsy-related complications. Therefore, we think that the reference significance of preoperative biopsy requires further evaluation, and should be combined with iodine staining, narrow band imaging with magnifying endoscopy (ME-NBI), and radiological examination.

Postoperative infection, bleeding and perforation are common in ESD procedure. Previous studies reported the bleeding and perforation rates of ESD to be 0-6% and 1.7%-4%[20-22], respectively. In our study, the total bleeding rate and perforation rate associated with ESTD were 8.04% and 1.93%, respectively. The significant bleeding that need postoperative hemostatic treatment is relatively low (1.61%), indicating that ESTD is a safe treatment method for superficial esophageal squamous cell carcinoma and precancerous lesions. 30 (9.65%) patients had postoperative infection. There are no available studies that have reported on post-ESD infection, although it is relatively common especially for the elderly. We guess that the infection is caused by the patient hypoimmunity and the history of previous pulmonary disease or inhalation pneumonia related to anesthesia; however, further studies are needed to confirm this etiology.

The esophageal stricture and positive margin are serious complications of ESTD procedure, and the incidence rates found in our study were 14.79% (46/311) and 15.76% (49/311), respectively. It was reported that the circumference level and the area of the lesion are risk factors for esophageal stricture[23,24]. The incidence rate of esophageal stricture in patients with circumference level > 3/4 is above 70%-90%[25,26]. When the lesion area is large enough, the artificial esophageal ulcer causes excess absence of epithelial cells and results in fibrous repair in the submucosa[27], which is the primary cause of esophageal stricture. To prevent esophageal stricture, the administration of steroids is useful, as previously reported[28,29], while endoscopic balloon dilation and esophageal stent implantation can also be options[30,31]. For positive margin, previous studies reported its incidence after ESD to be 3%-17%[18,32,33]. Wen reported that the lesion area and invasion depth are risk factors of positive margin[33], and hypothesized that a greater lesion area and deeper invasion level corresponded to higher positive rates of the incisal margin. When treating large and multiple lesions, the risk of positive margin is relatively high, and thus accurate preoperative labeling and intraoperative complete resection are important. There are no standard guidelines to address positive margin after endoscopic resection; therefore, we recommended additional surgery for all patients in our study with positive basal margin, horizontal margin carcinoma involvement and vascular invasion; however, several patients refused and entered the follow up cohort. No residual or recurrent tumor was observed during the follow-up period.

The present study is the largest sample research of ESTD technique to date, and our observation indicators are complete, the follow-up period is long, the results are credible and there is strong reference significance in clinical work. Moreover, our study also performed a detailed evaluation of postoperative pathology and emphasized its guiding role in the postoperative management of the patients. However, this study has several limitations. Firstly, this was a retrospective study and thus has inherent case selection bias. Secondly, this was a single center study; therefore, the operation level of ESTD in this study cannot be fully represented in whole.

In conclusion, ESTD for superficial esophageal squamous cell carcinoma and precancerous lesions is effective and safe, exhibiting high en bloc resection rate, as well as low bleeding and perforation rates. When using ESTD to resect large mucosal lesions, the incidence of postoperative esophageal stricture and positive margin is high, and thus other effective preventative measures should be considered. We also observed preoperative biopsies cannot represent the whole specimen while half of the biopsies’ pathology upgraded after ESTD procedure; therefore, the choice of therapy cases should be made cautiously before ESTD.

**ARTICLE HIGHLIGHTS**

***Research background***

Endoscopic submucosal dissection (ESD) is becoming the standard treatment for early gastrointestinal cancers, as it has a higher en bloc resection rate and a lower recurrence rate than endoscopic mucosal resection (EMR). However, when treating large mucosal lesions, ESD always faces many difficulties, such as multiple submucosal injections times, long procedure time and low complete resection rate. To overcome these difficulties, a modified technique named endoscopic submucosal tunnel dissection (ESTD) has been proposed. Compared with ESD, ESTD could reduce the number of submucosal injections, shorten the procedure time, increase the resection speed, and reduce the injury of the muscular layer. However, there are no studies that verify the feasibility of ESTD in superficial esophageal squamous cell carcinoma (ESCC) and precancerous lesions in a large sample.

***Research motivation***

To our knowledge, the present study is the largest sample research of ESTD technique to date, and our observation indicators are complete, the follow-up period is long, the results are credible and there is strong reference significance in clinical work.

***Research objectives***

This study aims to evaluate the clinical outcomes of patients who underwent ESTD for ESCC and precancerous lesions.

***Research methods***

ESTD was performed in 289 patients with 311 lesions. The clinical outcomes of the patients and pathological features of the lesions were retrospectively reviewed.

***Research results***

A total of 311 lesions were included. The en bloc rate, complete resection rate and curative resection rate were 99.04%, 81.28% and 78.46%, respectively. The ESTD procedure time was 102.4 ± 35.1 min, the mean hospitalization time was 10.3 ± 2.8 d and the average expenditure was 3766.5 ± 846.5 dollars. The intraoperative bleeding rate, postoperative bleeding rate, the perforation rate, and the postoperative infection rate were 6.43%, 1.61%, 1.93%, and 9.65%, respectively. Esophageal stricture and positive margin were severe adverse events with an incidence rate of 14.79% and 15.76%. No tumor recurrence occurred during the follow-up period.

***Research conclusions***

ESTD for ESCC and precancerous lesions is feasible and safety relatively, but the rate of esophageal stricture and positive margin is high for large mucosal lesions.

***Research perspectives***

The present study is a retrospective study to describe the general characteristics of ESTD. In the future, case control studies and prospective studies are considered necessary to further evaluate the feasibility and safety of ESTD for treating ESCC and precancerous lesions.

**REFERENCES**

1 **Lian J**, Chen S, Zhang Y, Qiu F. A meta-analysis of endoscopic submucosal dissection and EMR for early gastric cancer. *Gastrointest Endosc* 2012; **76**: 763-770 [PMID: 22884100 DOI: 10.1016/j.gie.2012.06.014]

2 **Ishihara R**, Iishi H, Uedo N, Takeuchi Y, Yamamoto S, Yamada T, Masuda E, Higashino K, Kato M, Narahara H, Tatsuta M. Comparison of EMR and endoscopic submucosal dissection for en bloc resection of early esophageal cancers in Japan. *Gastrointest Endosc* 2008; **68**: 1066-1072 [PMID: 18620345 DOI: 10.1016/j.gie.2008.03.1114]

3 **Pimentel-Nunes P**, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, Amato A, Berr F, Bhandari P, Bialek A, Conio M, Haringsma J, Langner C, Meisner S, Messmann H, Morino M, Neuhaus H, Piessevaux H, Rugge M, Saunders BP, Robaszkiewicz M, Seewald S, Kashin S, Dumonceau JM, Hassan C, Deprez PH. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; **47**: 829-854 [PMID: 26317585 DOI: 10.1055/s-0034-1392882]

4 **Maeda Y**, Hirasawa D, Fujita N, Obana T, Sugawara T, Ohira T, Harada Y, Yamagata T, Suzuki K, Koike Y, Yamamoto Y, Kusaka Z, Noda Y. A pilot study to assess mediastinal emphysema after esophageal endoscopic submucosal dissection with carbon dioxide insufflation. *Endoscopy* 2012; **44**: 565-571 [PMID: 22407383 DOI: 10.1055/s-0031-1291664]

5 **Linghu E**, Feng X, Wang X, Meng J, Du H, Wang H. Endoscopic submucosal tunnel dissection for large esophageal neoplastic lesions. *Endoscopy* 2013; **45**: 60-62 [PMID: 23254407 DOI: 10.1055/s-0032-1325965]

6 **Tsao SK**, Toyonaga T, Morita Y, Fujita T, Hayakumo T, Azuma T. Modified fishing-line traction system in endoscopic submucosal dissection of large esophageal tumors. *Endoscopy* 2011; **43** Suppl 2: E119 [PMID: 21425004 DOI: 10.1055/s-0030-1256148].]

7 **Xie X**, Bai JY, Fan CQ, Yang X, Zhao XY, Dong H, Yang SM, Yu J. Application of clip traction in endoscopic submucosal dissection to the treatment of early esophageal carcinoma and precancerous lesions. *Surg Endosc* 2017; **31**: 462-468 [PMID: 27126625 DOI: 10.1007/s00464-016-4939-1]

8 **Koike Y**, Hirasawa D, Fujita N, Maeda Y, Ohira T, Harada Y, Suzuki K, Yamagata T, Tanaka M. Usefulness of the thread-traction method in esophageal endoscopic submucosal dissection: randomized controlled trial. *Dig Endosc* 2015; **27**: 303-309 [PMID: 25357187 DOI: 10.1111/den.12396]

9 **Linghu E**.Therapeutics of Digestive Endoscopic Tunnel Technique. Berlin, Springer Netherlands, 2014

10 **Huang R**, Cai H, Zhao X, Lu X, Liu M, Lv W, Liu Z, Wu K, Han Y. Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal squamous cell carcinoma: a propensity score matching analysis. *Gastrointest Endosc* 2017; **86**: 831-838 [PMID: 28286094 DOI: 10.1016/j.gie.2017.03.001]

11 **Wang J**, Qin JY, Guo TJ, Gan T, Wang YP, Wu JC. [The Efficiency and Complications of ESD and ESTD in the Treatment of Large Esophageal Mucosal Lesions]. *Sichuan Da Xue Xue Bao Yi Xue Ban* 2015; **46**: 896-900 [PMID: 26867327]

12 **Zhai Y**, Linghu E, Li H, Qin Z, Feng X, Wang X, Du H, Meng J, Wang H, Zhu J. [Comparison of endoscopic submucosal tunnel dissection with endoscopic submucosal dissection for large esophageal superficial neoplasms]. *Nan Fang Yi Ke Da Xue Xue Bao* 2014; **34**: 36-40 [PMID: 24463113]

13 **Gan T**, Yang JL, Zhu LL, Wang YP, Yang L, Wu JC. Endoscopic submucosal multi-tunnel dissection for circumferential superficial esophageal neoplastic lesions (with videos). *Gastrointest Endosc* 2016; **84**: 143-146 [PMID: 26828761 DOI: 10.1016/j.gie.2016.01.049]

14 **Japan Esophageal Society.**. Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus* 2017; **14**: 1-36 [PMID: 28111535 DOI: 10.1007/s10388-016-0551-7].]

15 . The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-S43 [PMID: 14652541]

16 **Loizou LA**, Grigg D, Atkinson M, Robertson C, Bown SG. A prospective comparison of laser therapy and intubation in endoscopic palliation for malignant dysphagia. *Gastroenterology* 1991; **100**: 1303-1310 [PMID: 1707386]

17 **Qumseya BJ**, Wolfsen C, Wang Y, Othman M, Raimondo M, Bouras E, Wolfsen H, Wallace MB, Woodward T. Factors associated with increased bleeding post-endoscopic mucosal resection. *J Dig Dis* 2013; **14**: 140-146 [PMID: 23134152 DOI: 10.1111/1751-2980.12002]

18 **Joo DC**, Kim GH, Park DY, Jhi JH, Song GA. Long-term outcome after endoscopic submucosal dissection in patients with superficial esophageal squamous cell carcinoma: a single-center study. *Gut Liver* 2014; **8**: 612-618 [PMID: 25368748 DOI: 10.5009/gnl13130]

19 **Zhai YQ**, Li HK, Linghu EQ. Endoscopic submucosal tunnel dissection for large superficial esophageal squamous cell neoplasms. *World J Gastroenterol* 2016; **22**: 435-445 [PMID: 26755889 DOI: 10.3748/wjg.v22.i1.435]

20 **Oyama T**, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005; **3**: S67-S70 [PMID: 16013002]

21 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. *Gastrointest Endosc* 2009; **70**: 860-866 [PMID: 19577748 DOI: 10.1016/j.gie.2009.04.044]

22 **Sohara N**, Hagiwara S, Arai R, Iizuka H, Onozato Y, Kakizaki S. Can endoscopic submucosal dissection be safely performed in a smaller specialized clinic? *World J Gastroenterol* 2013; **19**: 528-535 [PMID: 23382632 DOI: 10.3748/wjg.v19.i4.528].]

23 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. *Endoscopy* 2009; **41**: 661-665 [PMID: 19565442 DOI: 10.1055/s-0029-1214867]

24 **Katada C**, Muto M, Manabe T, Boku N, Ohtsu A, Yoshida S. Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. *Gastrointest Endosc* 2003; **57**: 165-169 [PMID: 12556777]

25 **Ezoe Y**, Muto M, Horimatsu T, Morita S, Miyamoto S, Mochizuki S, Minashi K, Yano T, Ohtsu A, Chiba T. Efficacy of preventive endoscopic balloon dilation for esophageal stricture after endoscopic resection. *J Clin Gastroenterol* 2011; **45**: 222-227 [PMID: 20861798 DOI: 10.1097/MCG.0b013e3181f39f4e]

26 **Hashimoto S**, Kobayashi M, Takeuchi M, Sato Y, Narisawa R, Aoyagi Y. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. *Gastrointest Endosc* 2011; **74**: 1389-1393 [PMID: 22136782 DOI: 10.1016/j.gie.2011.07.070]

27 **Honda M**, Nakamura T, Hori Y, Shionoya Y, Yamamoto K, Nishizawa Y, Kojima F, Shigeno K. Feasibility study of corticosteroid treatment for esophageal ulcer after EMR in a canine model. *J Gastroenterol* 2011; **46**: 866-872 [PMID: 21597933 DOI: 10.1007/s00535-011-0400-3]

28 **Ratone JP**, Bories E, Caillol F, Pesenti C, Godat S, Poizat F, Cassan C, Giovannini M. Oral steroid prophylaxis is effective in preventing esophageal strictures after large endoscopic resection. *Ann Gastroenterol* 2017; **30**: 62-66 [PMID: 28042239 DOI: 10.20524/aog.2016.0085]

29 **Yamaguchi N**, Isomoto H, Nakayama T, Hayashi T, Nishiyama H, Ohnita K, Takeshima F, Shikuwa S, Kohno S, Nakao K. Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Gastrointest Endosc* 2011; **73**: 1115-1121 [PMID: 21492854 DOI: 10.1016/j.gie.2011.02.005]

30 **Sato H**, Inoue H, Kobayashi Y, Maselli R, Santi EG, Hayee B, Igarashi K, Yoshida A, Ikeda H, Onimaru M, Aoyagi Y, Kudo SE. Control of severe strictures after circumferential endoscopic submucosal dissection for esophageal carcinoma: oral steroid therapy with balloon dilation or balloon dilation alone. *Gastrointest Endosc* 2013; **78**: 250-257 [PMID: 23453294 DOI: 10.1016/j.gie.2013.01.008]

31 **Yano T**, Yoda Y, Nomura S, Toyosaki K, Hasegawa H, Ono H, Tanaka M, Morimoto H, Horimatsu T, Nonaka S, Kaneko K, Sato A. Prospective trial of biodegradable stents for refractory benign esophageal strictures after curative treatment of esophageal cancer. *Gastrointest Endosc* 2017; **86**: 492-499 [PMID: 28137598 DOI: 10.1016/j.gie.2017.01.011]

32 **Repici A**, Hassan C, Carlino A, Pagano N, Zullo A, Rando G, Strangio G, Romeo F, Nicita R, Rosati R, Malesci A. Endoscopic submucosal dissection in patients with early esophageal squamous cell carcinoma: results from a prospective Western series. *Gastrointest Endosc* 2010; **71**: 715-721 [PMID: 20363414 DOI: 10.1016/j.gie.2009.11.020]

33 **Wen J**, Linghu E, Yang Y, Liu Q, Wang X, Du H, Wang H, Meng J, Lu Z. Relevant risk factors and prognostic impact of positive resection margins after endoscopic submucosal dissection of superficial esophageal squamous cell neoplasia. *Surg Endosc* 2014; **28**: 1653-1659 [PMID: 24380990 DOI: 10.1007/s00464-013-3366-9]

**P-Reviewer:** Kosugi S, Ide E **S-Editor:** Wang XJ

**L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** China

**Peer-review report classification**

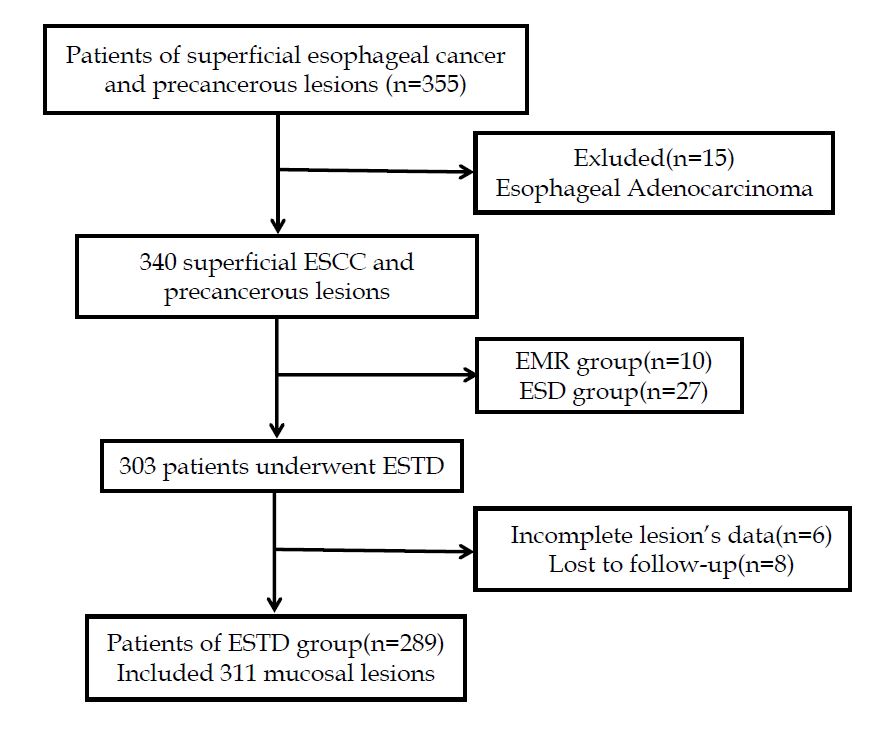
Grade A (Excellent): 0

Grade B (Very good): B

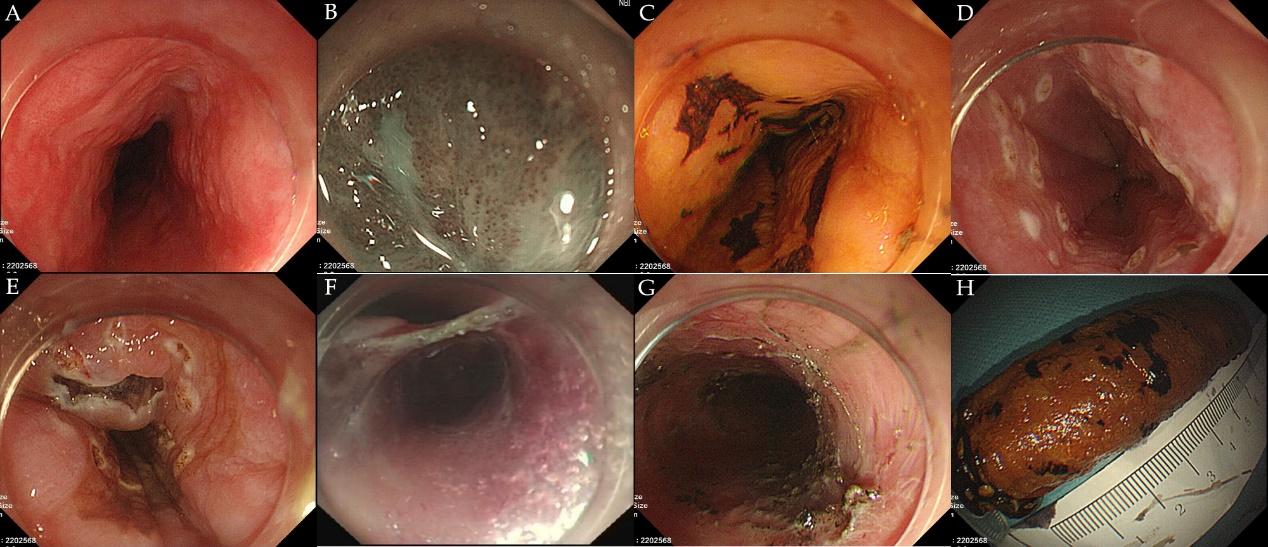
Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0



**Figure 1 Flowchart of enrollment process.**



**Figure 2 Endoscopic submucosal tunnel dissection procedures.** A: Lesion was detected under white light endoscopy; B: Lesion was observed under NBI; C: Lesion was observed under iodine staining; D: The margin of the lesion was marked; E: Anal-side and oral-side incisions after submucosal injection; F: Creating the submucosal tunnel and resecting the lesion; G: The artificial wound after endoscopic submucosal tunnel dissection; H: The *in vitro* specimen encircled in the body of a syringe after iodine staining.

**Table 1 Baseline characteristics of 311 lesions treated with endoscopic submucosal tunnel dissection *n* (%)**

|  |  |
| --- | --- |
| **Category** | **ESTD (*n* = 311)** |
| Sex, male/female | 213/98 |
| Age, yr, mean (range) | 61.4 ± 8.1 (40-83) |
| Tumor location |  |
| Upper third | 24 (7.72) |
| Middle third | 200 (64.31) |
| Lower third | 87 (27.97) |
| Paris classification |  |
| 0-Ⅰ | 18 (5.79) |
| 0-Ⅱa | 111 (35.69) |
| 0-Ⅱb | 94 (30.23) |
| 0-Ⅱc | 35 (11.25) |
| 0-Ⅱa-Ⅱc | 50 (16.08) |
| 0-Ⅲ | 3 (0.96) |
| Circumferential level |  |
| ≤ 1/4 | 11 (3.54) |
| ≤ 1/2 | 163 (52.41) |
| ≤ 3/4 | 65 (20.90) |
| ≤ 7/8 | 41 (13.18) |
| ≤ 1 | 31 (9.97) |

ESTD: Endoscopic submucosal tunnel dissection.

**Table 2 Pre-endoscopic submucosal tunnel dissection and post-endoscopic submucosal tunnel dissection pathology *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Pathology** | **Pre-ESTD** | **Post-ESTD** | **Pre-ESTD and Post-ESTD coincidence** |
| Inflammation | 0 | 3 (0.96) | 0 |
| LGIN | 67 (21.54) | 43 (13.83) | 36 (11.57) |
| HGIN | 159 (51.13) | 52 (16.72) | 37 (11.90) |
| M1 | 74 (23.79) | 74 (23.79) | 18 (5.79) |
| M2 | 11 (3.54) | 47 (15.11) | 3 (0.96) |
| M3 | 0 | 51 (16.40) | 0 |
| SM1 | 0 | 23 (7.40) | 0 |
| > SM1 | 0 | 18 (5.79) | 0 |

ESTD: Endoscopic submucosal tunnel dissection; LGIN: Low-grade intraepithelial neoplasia; HGIN: High-grade intraepithelial neoplasia; M1: Carcinoma in situ; M2: Carcinoma infiltrated to laminae propria; M3: Carcinoma infiltrated to muscularis mucosae; SM1: Submucosal invasion < 200 μm; SM2: Submucosal invasion > 200 μm.

**Table 3 Endoscopic submucosal tunnel dissection procedure characteristics *n* (%)**

|  |  |
| --- | --- |
| **Category** | **ESTD (*n* = 311)** |
| Specimen area, cm2, mean ± SD | 14.1 ± 3.6 |
| Tumor width diameter, cm, mean ± SD | 3.1 ± 0.6 |
| Tumor length diameter, cm, mean ± SD | 4.2 ± 0.9 |
| Procedure time, min, mean ± SD | 102.4 ± 35.3 |
| Dissection speed, mm2/ min, mean ± SD | 18.6 ± 2.1 |
| En bloc resection | 308 (99.04) |
| R0 resection | 259 (81.28) |
| Curative resection | 244 (78.46) |
| Hospitalization day, d, mean ± SD | 10.3 ± 2.8 |
| Hospitalization expense, dollars, mean ± SD | 3766.5 ± 846.5 |

ESTD: Endoscopic submucosal tunnel dissection.

**Table 4 Endoscopic submucosal tunnel dissection-related complications *n* (%)**

|  |  |
| --- | --- |
| **Category** | **ESTD (*n* = 311)** |
| Post-operative infection | 30 (9.65) |
| Bleeding |  |
| Intraoperative bleeding | 20 (6.43) |
| Postoperative bleeding | 5 (1.61) |
| Muscular injury | 98 (31.51) |
| Perforation | 6 (1.93) |
| Esophageal stricture | 46 (14.79) |
| Positive margin |  |
| Horizontal margin | 35 (11.25) |
| Vertical margin | 10 (3.22) |
| Horizontal and vertical margin | 4 (1.29） |
| Lymphovascular invasion | 12 (3.86) |

ESTD: Endoscopic submucosal tunnel dissection.