学位論文

Optimal Selection of Endoscopic Resection in Patients with Esophageal Squamous Cell Carcinoma: Endoscopic Mucosal Resection vs Endoscopic Submucosal Dissection According to Lesion Size

(食道表在癌に対する内視鏡治療　腫瘍径からみた EMR と ESD の比較検討)

福島県立医科大学大学院医学研究科

消化器内科学講座

川島　一公

Abstract

Background: En bloc resection is essential for accurate pathological evaluation in patients with superficial esophageal squamous cell carcinoma (SESCC). This retrospective study aimed to clarify optimal treatment selection of endoscopic resection according to lesion size.

Patients and methods: A total of 760 patients underwent endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) between January 2011 and December 2015. Among them, this retrospective study included 196 solitary index SESCC lesions ≤20mm, with the deepest invasion to the mucosa or submucosa. The lesions were classified according to size measured via endoscopy as follows; Group A: lesions ≤10mm, Group B: lesions ≥11mm but ≤15mm, and Group C: lesions ≥16mm but ≤20mm. The short- and long-term outcomes were investigated for EMR and ESD subgroups.

Results: In patients undergoing EMR and ESD, en bloc resection rates for Group A and B were not different (98.8% vs 100%, 93.3% vs 100%, respectively). However, the en bloc resection rate was significantly lower in EMR than that in ESD for Group C (64.3% vs 100%, $p < 0.001$). Furthermore, the use of adjunctive ablative therapy rate was significantly higher in EMR than that in ESD in Group C (35.7% vs 0%, $p < 0.001$). The 5-year cumulative local recurrence rate of Group C was significantly higher than that of Group A+B after EMR ($p < 0.01$).

Conclusion: EMR was an adequate treatment for SESCC lesions ≤15mm. On the other hand, ESD could be necessary to achieve en bloc resection for lesions ≥16mm to avoid local recurrence.

Key words: adjunctive ablative therapy, en bloc resection, endoscopic mucosal resection, endoscopic submucosal dissection, superficial esophageal squamous cell carcinoma

Introduction

The detection of superficial esophageal squamous cell carcinoma (SESCC) has substantially improved with the routine use of narrow band imaging and chromoendoscopy with iodine staining [1, 2]. When esophageal squamous cell carcinomas are confined to the mucosal epithelium or the lamina propria (cT1a-EP or LPM), SESCC is only rarely associated with lymph-node metastasis. Therefore, curative resection can be achieved via endoscopy without the need for additional treatments. On the other hand, lesions extending up to the muscularis mucosae (cT1a-MM) or slightly infiltrating the submucosa (up to 200μm, cT1b-SM1) are relative indications for mucosal resection; they have an elevated risk of lymph-node metastasis [3, 4]. The frequency of lymph node metastasis was reported 0% for pT1a-EP/LPM cases, 33% for pT1a–MM cases, 29% for pT1b-SM1 cases, and 37% for pT1b–SM2 cases [5]. According to Guideline for Endoscopic submucosal dissection/endoscopic mucosal resection for esophageal cancer, en bloc resection is recommended for accurate pathological evaluation [6]. Endoscopic resection is recommended for cT1a-EP/LPM SESCC with non-circumferential lesions and the entire circumference lesions with a major axis length ≤50 mm [3, 4, 6]. For the size of SESCC ≤20mm, endoscopic mucosal resection (EMR) is relatively easily performed and efficient. However, the specimen size was limited owing to the size of snare. In contrast, endoscopic submucosal dissection (ESD) allows for en bloc resection regardless of lesion size, however, it is technically challenging and time-consuming. Therapeutic methods vary based on institutional preferences as selection of endoscopic therapy for SESCC ≤20mm have not currently standardized [3, 4, 6]. To clarify optimal treatment selection of endoscopic resection according to the lesion size, we aimed to compare the short- and long-term outcomes between EMR and ESD in patients with SESCC retrospectively.

Patients

A total of 858 SESCCs in 760 patients were treated by EMR or ESD from January 2011 to December 2015 at National Cancer Center Hospital. We identified 196 lesions in 196 patients who met our inclusion criteria. The inclusion criteria were the followings: (1) histologically proven squamous cell carcinoma, (2) a solitary, index SESCC 20mm or smaller in size based on endoscopic measurement, (3) a tumor invasion depth extending up to 200μm below the lower border of the muscularis mucosae endoscopically and (4) no prior endoscopic or systemic therapy (Fig.1). Long-term results included patients with follow up periods of more than 1 year and excluded patients with pT1a-MM with positive lymphovascular invasion or pT1b-SM1/SM2. The lesions were classified according to size as follows: Group A: lesions 10mm or smaller, Group B: lesions 11mm or larger but smaller than 15mm, and Group C: lesions 16mm or larger but smaller 20mm. The lesion size was endoscopically measured before treatment relative to the diameter of biopsy forceps or the size of snares. In terms of short-term outcomes; the en bloc and R0 resection rates, procedure time, need for adjunctive ablative therapy, and adverse event rate were assessed among these groups. Long-term outcomes included 5-year cumulative local recurrence rate, 5-year overall survival (OS) rate, 5-year disease-specific survival (DSS) rate. Written informed consent was obtained from all patients before endoscopic resections. This study was approval for Institutional Review Board at our hospital. This study was registered with University Hospital Medical Information Network (UMIN000038042).

Methods

In this study, endoscopic resection was indicated for SESCCs clinically confined to the indication lesions (cT1a-EP or LPM), and relative indication lesions (cT1a-MM or cT1b-SM1) as mentioned before. EMR or ESD was performed by attending endoscopists or residents supervised by attending endoscopists, and the selection of endoscopic resection method was made at the discretion of the attending endoscopist. En bloc resection was attempted in all cases and piecemeal resection was not scheduled.

All treatments were performed with the patients under intravenous sedation with pentazocine and midazolam, propofol or both midazolam and propofol. The sedative agents were selected at the discretion of the attending endoscopist. Monitor anesthesia care (MAC) using propofol and fentanyl could also be selected as we reported before [7]. For cases deemed suitable for EMR, the cap-assisted EMR method was used. (Fig. 2) [8, 9]. EMR was performed with the use of a single-channel endoscope (H260; Olympus Optical Co. Ltd, Tokyo, Japan). Prior to EMR, chromoendoscopy with iodine staining was performed to determine the borders of the tumor, and the outer periphery of the lesion was marked by a tip of designed crescent-shaped electrocautery snare (SD-221L-25; Olympus Tokyo, Japan). Saline with diluted indigo carmine was injected into the submucosa via injection needle. The snare was opened in the oblique transparent cap with an internal circumferential ridge (MAJ-290; Olympus Tokyo, Japan). The lesion was suctioned into the cap, and then captured and resected by the snare. When residual tumor was suspected post-EMR, ablative therapy with argon plasma coagulation, tip of snare or hemostatic forceps was performed to remove all macroscopically visible tumor at the discretion of the attending endoscopist.

ESD was performed using a single-channel esophagogastroduodenoscope with water-jet system (GIF-Q260J; Olympus Optical Co. Ltd, Tokyo, Japan) (Fig. 3) [10]. A disposable transparent attachment (TOP Endoscopic Hood; TOP Tokyo, Japan) was fitted onto the tip of the endoscope to facilitate ESD. Before the procedure, chromoendoscopy with iodine staining was carried out to determine the borders of the cancer area, and the outer periphery of the lesion was marked using the tip of a dual knife (KD-650U; Olympus Tokyo, Japan). Saline with diluted indigo carmine was first injected into the submucosa sufficiently at the proximal and distal sides, followed by sodium hyaluronate solution with dissolved saline. Using a dual knife and IT knife nano (KD-612U; Olympus Tokyo, Japan), a mucosal incision at the proximal and distal ends was made and a communication between the proximal and distal sides against the force of gravity to get the lesion away from the area water pool. The endoscope entered the submucosal layer from the proximal side, and submucosal dissection was primarily performed with an IT knife nano. The clip line traction method was used as needed to facilitate submucosal dissection as previously described [11].

Histologic assessment

The resected specimens were immersed in 4% formalin for 24-48 hours. The specimens were embedded in 10% paraffin, cut in 2-mm slices, and stained with hematoxylin and eosin. The histological findings were classified according to the Japanese Classification of Esophageal Cancer [12], and all the specimens were examined by two experienced pathologists. When the diagnosis of lymphatic and venous involvement was inconclusive using HE-stained, Elastica van Gieson (EVG) staining for vascular invasion and antibody D2-40 staining for lymphatic invasion was additionally performed. The depth of infiltration was classified as follows: EP, an epithelial tumor;

LPM, a mucosal tumor with invasion to the lamina propria; MM, a mucosal tumor that almost reaches the muscularis mucosae; SM1, a tumor extends up to 200μm below the lower border of the lamina muscularis mucosae; SM2, a tumor that extends more than 200μm below the lower border of the muscularis mucosae [4]. High-grade intraepithelial neoplasia (HGIN) was classified as EP in this study.

Curability

In this present study, we defined en bloc resection as the removal of the entire lesion in one piece. R0 resection was defined histologically as en bloc resection with tumor-free horizontal and vertical margins. Additional treatment was generally indicated for lesion with lymphovascular invasion or any submucosal invasion. Lesions (pT1a-EP or LPM) with horizontal margin positivity underwent rigorous endoscopic surveillance. Curative-resection was defined as the R0 resection of the mucosal resection with no lymphovascular invasion. Non-curative resection was defined as those with lymphovascular invasion and/or any submucosal invasion. Non-curative resection cases received additional treatments or follow-up.

Adverse events

Intraprocedural perforation was diagnosed when mediastinal connective tissue was observed during the procedure. Delayed perforation was diagnosed via the presence of free air with computed tomography after endoscopic resection. Delayed bleeding was defined as bleeding requiring postoperative endoscopic hemostatic treatment, such as thermocoagulation or endoscopic clipping. Postoperative esophageal stricture was diagnosed when a patient developed dysphagia and a standard endoscope (8.9-9.8mm in diameter) was unable to pass through the stricture.

Follow up

After endoscopic resection, an esophagogastroduodenoscopy with chromoendoscopy via iodine staining was carried out every 6 or 12 months at the discretion of referring endoscopists. Local recurrence was diagnosed when an iodine-unstained area was detected at an endoscopic resection scar, and cancer cells were histologically verified by a biopsy specimen. When distinct lesions away from the post- resection scar were detected, they were defined as metachronous lesions if found after 12 months of the index resection [6].

Statistical analysis

Categorical variables were compared using the Chi-square test or Fisher's exact test, and quantitative variables were by using the Mann-Whitney U test. A p value less than 0.05 was considered statistically significant. The 5-year cumulative local recurrence rate, 5-year OS rate and the 5-year DSS rate were calculated by Kaplan-Meier analysis. The long-term outcomes were evaluated in patients with curative resection with more than 1 year follow up and patients that received no additional therapy post-resection (i.e. chemoradiotherapy and additional surgery). OS was measured from the date of endoscopic resection to the date of death or the date of the latest confirmation of survival. DSS was measured from the date of endoscopic resection to the date of death from SESCC. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [13]. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

The clinicopathological features of 196 SESCCs are shown in the Table 1. There were no significant differences in patient characteristics, sex, age, and tumor locations between EMR and ESD groups. ESD was significantly more commonly performed in 2013-2015 than in 2011-2012 ($p<0.01$). Furthermore, EMR was performed more frequently than ESD in Group A, however, ESD was more commonly performed in Group C. The median procedure time for ESD was significantly longer than that of EMR (15minutes vs 60minutes, $p<0.001$). Median follow up periods of EMR was significantly longer than that of ESD (56 months vs 46 months, $p=0.04$). MAC and propofol sedation were more frequently used in the ESD group, and intraoperative sedation was adequately performed in both EMR and ESD groups.

En bloc resection rates of ESD were 100% in all groups (Table 2). In Group A and B, there were no significant difference in en bloc resection rates between the EMR and ESD methods, however, en bloc resection rate of EMR was significantly lower than that of the ESD in Group C (64.3% vs 100%, p

<0.001). In total, R0 resection rate of the EMR groups was also significantly lower than that of the ESD groups (70.2% vs 89.1%, p <0.01). Among the groups, there were no difference in R0 resection rates between EMR and ESD in Groups A and B. In Group C, however, R0 resection rate via EMR was significantly lower than that of ESD (28.6% vs 91.7%, p<0.001). Attendings performed 44 EMRs and 37 ESDs, and residents performed 97 EMRs and 18 ESDs, respectively. ESD was more commonly performed by attending endoscopists than residents (p<0.001). The R0 resection rates of attendings and residents were 72.7% (32/44) and 69.1% (67/97) in the EMR group (p=0.66), and 91.9% (34/37) and 83.3% (15/18) in the ESD group (p=0.29), respectively. There were no significant differences between the two groups.

Given the 100% en bloc resection rate in patients treated with ESD, none required adjunctive ablative therapy post-resection (Table 3). In Groups A and B, there were no significant difference in the need for adjunctive ablative therapy between the EMR and ESD methods. However, in Group C, the use of adjunctive ablative therapy was significantly higher in the EMR group (35.7% vs 0%, p <0.001). No significant differences in adverse events were noted between resection methods across the groups (Table 4). Adverse events occurred in three patients. Among them, one perforation and one stricture occurred in procedures performed by attending physicians and one case of delayed bleeding occurred in a procedure performed by a resident. All cases were managed conservatively with endoscopic treatments.

Among the 48 non-R0 resections, 43 had positive horizontal margin, 3 had positive vertical margin, and 2 had both positive horizontal and vertical margin. As for the 5 lesions with positive vertical margin, 3 lesions were SM2 treated by ESD, and 2 were LPM but treated by piecemeal EMR. The median difference in the lesion size before and after treatment was 2 mm (range -17-+10mm, interquartile [IQR] 0-3mm) for the EMR group and 2 mm (range -7-+9mm, IQR 0-5mm) for the ESD group.

Of the 196 patients evaluated in this study, we identified 160 lesions in 160 patients that met our inclusion criteria for evaluation of long-term outcomes. The numbers of patients treated with EMR and ESD in the long-term outcomes analysis were 120 and 40 respectively. A total of 36 patients were excluded from the analysis of long-term outcomes. Among them, 23 cases were followed within 1 year and 13 cases (EMR: 6 cases, ESD: 7 cases) were non-curative resected cases (6.6%, 13/196). Of the 13 cases, 10 cases underwent additional chemoradiotherapy and 2 were followed up, and 1 had additional surgical operation. At the median follow up periods of EMR and ESD were 58 months and 52 months respectively. There was no difference in the 5-year cumulative local recurrence rate between EMR and ESD (0.8% vs 0%, p=0.56). There was no local recurrence of EMR and ESD groups in Group A and B. However, one case with positive horizontal margin in Group C had a local recurrence 14.4 months post-EMR. This local recurrence was followed up without any additional treatment given the patient's history of advanced prostate cancer. In the sub-analysis between Group A+B and C, the median follow up periods of Group A+B and C after EMR were 58 months in the both groups. The 5-year cumulative local recurrence rates of EMR between Group A+B and Group C were 0% and 8.3% and those of ESD were 0% and 0% respectively. The cumulative local recurrence rate of Group C had a significantly higher than that of Group A+B ($p < 0.01$, Fig. 4).

In addition, 17 cases of metachronous esophageal cancer were recognized (8.7%, 17/196). These cases were treated with additional endoscopic resection and no recurrence has occurred. During the study period, no lymph node metastasis and no distant metastasis were observed for 160 patients. The 5-year OS rate in ESD groups was 100%, and that in EMR groups was exceeding 92%. The 5-year DSS rates in all groups were 100%. The 5-year OS rates of Group A+B and C after EMR were 97.1% and 91.7%, respectively. The 5-year OS rates were not significantly different between Group A+B and Group C (p=0.29, Fig. 5).

Discussion

This retrospective study aimed to clarify the optimal endoscopic treatment strategy for small SESCCs based on lesion size. In this report, there was no difference in short- and long-term results between EMR and ESD for lesions ≤15mm. No significant differences in adverse events were noted between resection methods across the groups. However, for lesions with 16-20mm, en bloc and R0 resection rates were significantly lower after EMR than those after ESD. Furthermore, the need for adjunctive ablative therapy in lesions with 16-20mm was significantly higher for EMR than that for ESD. Therefore, ESD is recommended to achieve en bloc resection for lesions with 16-20mm in the view of accurate pathological evaluation. The endoscopic lesion size was considerably consistent with pathologic lesion size and the difference was unlikely to influence the results of this study. Although there were some outliers, the overestimation and underestimation could be explained by adjacent low-grade intraepithelial neoplasia and mild iodine staining.

It has been reported that SESCC lesions larger than 20mm should be resected en bloc by ESD [14]. The endoscopic treatments of SESCC ≤20mm differs by facilities, as the selection of endoscopic therapy for esophageal cancer is not currently standardized. The procedure of EMR for SESCC is relatively straightforward and the median procedure time was significantly shorter in EMR compared to that of ESD for each groups. These results are consistent with previous reports [15-17]. EMR is considered to be reasonable treatment option for SESCC ≤15mm. The overall recurrence rate after EMR in this study was 0.8%, and this low local recurrence rate was consistent with a previous publication [18]. According to previous publications, the local recurrence rate of EMR is 3.1-26%, and the lesion size, multiple iodine unstained areas, and piecemeal resection have been reported as risk factors of local recurrence [14, 18-20].

Given our low local recurrence rate of EMR in our hospital, this may be accounted for by the fact that our current study was evaluating small lesions limited to 20 mm or less in size. In spite of R0 resection rates of EMR and ESD groups were low in this study, local recurrence was only 1 case post-ESD in Group C. This low local recurrence rate might be due to the cautery effect. In this study, EMR or ESD was performed by attending endoscopists or residents supervised by attending endoscopists. Although ESD was more commonly performed by attending endoscopists, and residents were well supervised by attending endoscopists. There were no significant differences in R0 resection rates of EMR and ESD between the two groups. Also, there was only one adverse event in ESD by the resident. Therefore, we believe that skill and experience of endoscopists did not influence the results of this study. Seventeen cases of metachronous esophageal carcinoma occurred, but all cases were managed by endoscopic treatment.

In previous publications, the 5-year OS rates for SESCC with cT1a-EP, LPM and MM was 79.5% for EMR and SESCC with cT1a-EP and LPM 95% for ESD [21, 22]. In this study, 5-year OS rate is as high as 92% for EMR and 100% for ESD, because in this study most lesions were cT1a-EP and LPM and we excluded patients that were treated with chemoradiotherapy after endoscopic resection. This study showed EMR could obtain short- and long-term results equivalent to ESD if the SESCC lesion was 15mm or less. The mains strengths of the current study were that each groups were classified by every 5mm and had longer follow up periods than previous publications. Furthermore, this study was examined in the same cohort study for short- and long-term results.

En bloc resection is very important for accurate pathological evaluation of the resected specimen and determination of necessity for additional treatment [3, 4]. Kakushima et al. [23] reported that ESD might be the best endoscopic resection method even for smaller SESCC lesions ≤20mm compared with EMR. Furthermore, Yamashita et al. [16] reported that EMR was more effective resection compared to ESD for lesions ≤10mm, on the other hand, Ishihara et al. [24] reported for lesions ≤15mm. This difference between these previous publications might be varied from the classified lesion size of each publication. In this study, there were no differences between EMR and ESD in the short-term outcomes for the en bloc and R0 resection rates for SESCC ≤15mm. In patients undergoing ESD, all lesions were resected as en bloc regardless of the size, however, rates of en-bloc and R0 resection via EMR for SESCC with 16-20mm were significantly lower owing to the snare size. Similarly, previous publications showed if the lesion size is greater than or equal to 20mm, en bloc resection rate is as low as 4.5-43.6% after EMR [14-16, 20].

Furthermore, in patients undergoing EMR, additional adjunctive ablation was performed more significantly for Group C than that for Group A+B (5.4% vs 35.7%, $p<0.001$). Considering short procedure time and low cost, EMR with adjunctive ablative therapy also appeared to be acceptable given favorable 5-year OS and DSS rate. However, 5-year cumulative local recurrence rate for Group C was significantly higher than that for Group A+B. Also incomplete endoscopic resection potentially will make accurate pathological diagnosis difficult. We believe en bloc resection is essential for lesion ≥16mm to avoid local recurrence and following additional treatment, and achieve precise histological assessment which is recommended by the guidelines. As far as we know, there has been no report about additional adjunctive ablation for SESCCs after endoscopic resection.

This study has some limitations. First, this was a single center, retrospective study. Second, the selection of EMR and ESD treatment was dependent on operator's preference. For instance, the resection method was greatly influenced by chronologic trends, and mirrored the technical development of ESD. Third, although local recurrence was defined as SESCC at an endoscopic resection scar, it is quite difficult to differentiate between a new lesion and local recurrence in case of SESCC with adjacent low-grade intraepithelial neoplasia. Forth, the proportion of patients with recurrence was small. Further prospective study is warranted to investigate the short- and long-term outcomes of EMR and ESD for lesions ≤20mm.

In conclusion, EMR was an adequate treatment for SESCC lesions ≤15mm. On the other hand, ESD could be necessary to achieve en bloc resection for lesions ≥16mm to avoid local recurrence.

Acknowledgments

The authors are grateful to Amar Manvar for linguistic revision and comments of this work. This work was supported in part by The National Cancer Center Research and Development Fund (28-K-1 and 29-A-13).

Disclosure Statement

The authors declare no conflicts of interest

Authors' contributions

KK contributed to the conception and design of the study, analysis and interpretation of the data, and drafting of the manuscript. SA, SN, HS, SY, IO, TH, HO and YS contributed to the conception and design of the study, interpretation of the data, and review of the manuscript. MK contributed to the doctor's evaluation and collection of the data. All authors read and approved the final manuscript.

Reference

1 Shimizu Y, Takahashi M, Mizushima T et al. Chromoendoscopy with iodine staining, as well as narrow-band imaging, is still useful and reliable for screening of early esophageal squamous cell carcinoma. Am J Gastroenterol. 2015; 110(1): 193-4.

2 Kuraoka K, Hoshino E, Tsuchida T, et al. Early esophageal cancer can be detected by screening endoscopy assisted with narrow-band imaging (NBI). Hepatogastroenterology 2009; 56(89): 63-6.

3 Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 1. Esophagus 2019; 16(1): 1-24.

4 Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. Esophagus 2019; 16(1): 25-43.

5 Akutsu Y, Uesato M, Shuto K, et al. The overall prevalence of metastasis in T1 esophageal squamous cell carcinoma: a retrospective

analysis of 295 patients. Ann Surg 2013; 257(6): 1032-8.

6 Ishihara R, Arima M, Iizuka T, et al. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. Dig Endosc. 2020; 32(4): 452-93.

7 Nonaka S, Kawaguchi Y, Oda I, et al. Safety and effectiveness of propofol-based monitored anesthesia care without intubation during endoscopic submucosal dissection for early gastric and esophageal cancers. Dig Endosc 2015; 27(6): 665-73.

8 Inoue H, Takeshita K, Hori H, et al. Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. Gastrointest Endosc 1993; 39(1): 58-62.

9 Ning B, Abdelfatah MM, Othman MO. Endoscopic submucosal dissection and endoscopic mucosal resection for early stage esophageal cancer. Ann Cardiothorac Surg 2017; 6(2): 88-98.

10 Oyama T, Tomori A, Hotta K, et al. Endoscopic submucosal dissection of early esophageal cancer. Clin Gastroenterol Hepatol 2005; 3: S67-70.

11 Abe S, Oda I, Suzuki H, et al. Insulated tip knife tunneling technique with clip line traction for safe endoscopic submucosal dissection of large

circumferential esophageal cancer. VideoGIE 2017; 2(12): 342-5.

12 Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. Esophagus 2017; 14(1): 37-65.

13 Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013; 48(3): 452-8.

14 Ishihara R, Iishi H, Takeuchi Y, et al. Local recurrence of large squamous-cell carcinoma of the esophagus after endoscopic resection. Gastrointest Endosc 2008; 67(6): 799-804.

15 Urabe Y, Hiyama T, Tanaka S, et al. Advantages of endoscopic submucosal dissection versus endoscopic oblique aspiration mucosectomy for superficial esophageal tumors. J Gastroenterol Hepatol 2011; 26(2): 275-80.

16 Yamashita T, Zeniya A, Ishii H, et al. Endoscopic mucosal resection using a cap-fitted panendoscope and endoscopic submucosal dissection as optimal endoscopic procedures for superficial esophageal carcinoma. Surg Endosc 2011; 25(8): 2541-6.

17 Takahashi H, Arimura Y, Hosokawa M, et al. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video).

Gastrointest Endosc 2010; 72(2): 255-64.

18 Esaki M, Matsumoto T, Hirakawa K, et al. Risk factors for local recurrence of superficial esophageal cancer after treatment by endoscopic mucosal resection. Endoscopy 2007; 39(1): 41-5.

19 Pech O, May A, Gossner L, et al. Curative endoscopic therapy in patients with early esophageal squamous-cell carcinoma or high-grade intraepithelial neoplasia. Endoscopy 2007; 39(1): 30-5.

20 Katada C, Muto M, Manabe T, et al. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. Gastrointest Endosc 2005; 61(2): 219-25.

21 Ono S, Fujishiro M, Niimi K, et al. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. Gastrointest Endosc 2009; 70(5): 860-6.

22 Katada C, Muto M, Momma K, et al. Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae--a multicenter retrospective cohort study. Endoscopy 2007; 39(9): 779-83.

23 Kakushima N, Fujishiro M. Endoscopic submucosal dissection for

gastrointestinal neoplasms. World J Gastroenterol 2008; 14(19): 2962-7.

24 Ishihara R, Iishi H, Uedo N, et al. Comparison of EMR and endoscopic submucosal dissection for en bloc resection of early esophageal cancers in Japan. Gastrointest Endosc 2008; 68(6): 1066-72.

Table

Table 1. Clinicopathological features of 196 superficial esophageal carcinoma in the EMR and ESD

	EMR (n = 141)	ESD (n = 55)	P value
Male / Female, n	118 / 23	44 / 11	0.54
Median age, years (range)	69 (45-88)	68 (37-86)	0.31
Years of EMR/ESD, n			< 0.001
2011-2012	77	13	
2013-2015	64	42	
Attending endoscopist/ resident, n	44 / 97	37 / 18	< 0.001
Sedation (MAC/Propofol/Midazolam/Propofol and Midazolam), n	4/62/74/1	15/37/3/0	< 0.001*
2011-2012	2/16/58/1	5/5/3/0	
2013-2015	2/46/16/0	10/32/0/0	
Location (Ce/Ut/Mt/Lt/Ae), n	2/21/85/27/6	1/7/36/10/1	0.91
Median lesion size, mm (range)	10 (1-20)	19 (8-20)	< 0.001
Endoscopic lesion size, n (%)			< 0.001
Group A: ≤10mm	82 (58.2)	5 (9.1)	
Group B: 11-15mm	45 (31.9)	14 (25.5)	
Group C: 16-20mm	14 (9.9)	36 (65.4)	
Median procedure times, minutes (range)	15 (3-60)	60 (24-140)	< 0.001

Depth of invasion			
(EP/LPM/MM/SM1/SM2), n	72/56/9/1/3	12/27/8/2/6	< 0.001
Median follow up period,			
months (range)	56 (0-94)	46 (0-86)	0.04

* P value: MAC and propofol vs Midazolam.

Ae, abdominal esophagus; Ce, cervical esophagus; EMR, endoscopic mucosal resection; EP, epithelial carcinoma; ER, endoscopic resection; ESD, endoscopic submucosal dissection; LPM, mucosal carcinoma with invasion to the lamina propria; Lt, lower thoracic esophagus; MAC, Monitored Anesthesia Care; MM, carcinoma invading the muscularis mucosae; Mt, middle thoracic esophagus; SCC, squamous cell carcinoma; SM1, carcinoma extending up to the 200μm below the lower border of the muscularis mucosae; SM2, carcinoma extending more than 200μm below the lower border of the muscularis mucosae; Ut, upper thoracic esophagus.

Table 2. Short-term outcomes after the EMR and ESD (n=196)

	EMR	ESD	P value
Median procedure time,			
Minutes (range)	**15 (3-60)**	**60 (24-140)**	**< 0.001**
Group A: ≤10mm	15 (3-40)	50 (24-70)	< 0.001
Group B: 11-15mm	15 (5-60)	60 (27-90)	< 0.001
Group C: 16-20mm	30 (10-60)	60 (25-140)	< 0.001
En bloc resection, % (n)	**90.8 (128/141)**	**100(55/55)**	**0.02**
Group A: ≤10mm	98.8 (81/82)	100 (5/5)	1
Group B: 11-15mm	93.3 (42/45)	100 (14/14)	0.32
Group C: 16-20mm	64.3 (5/14)	100 (36/36)	< 0.001
R0 resection, % (n)	**70.2 (99/141)**	**89.1 (49/55)**	**< 0.01**
Group A: ≤10mm	76.8 (63/82)	100 (5/5)	0.58
Group B: 11-15mm	71.1 (32/45)	78.6 (11/14)	0.58
Group C: 16-20mm	28.6 (4/14)	91.7 (33/36)	< 0.001

EMRC, endoscopic mucosal resection using a cap; ESD, endoscopic submucosal dissection.

Table 3. Adjunctive ablative therapy after the EMR and ESD (n=196)

	EMR, % (n)	ESD, % (n)	P value
Group A: ≤10mm	6.1 (5/82)	0 (0/5)	1
Group B: 11-15mm	4.4 (2/45)	0 (0/14)	0.43
Group C: 16-20mm	35.7 (5/14)	0 (0/36)	< 0.001
Total	8.5 (12/141)	0 (0/55)	0.03

When iodine unstaining area was suspected after endoscopic resection, the adjunctive ablation was performed additionally.

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

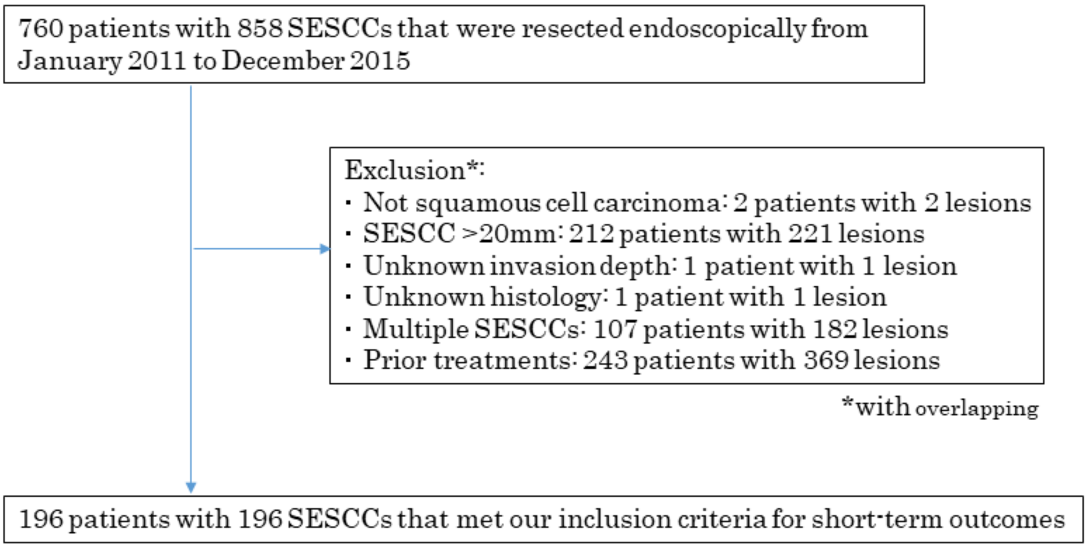
Table 4. Adverse events during and after the EMR and ESD (n=196)

	EMR	ESD	P value
Intraprocedural perforation, % (n)	0 (0/141)	0 (0/55)	1
Group A: ≤10mm	0 (0/82)	0 (0/5)	1
Group B: 11–15mm	0 (0/45)	0 (0/14)	1
Group C: 16–20mm	0 (0/14)	0 (0/36)	1
Delayed perforation, % (n)	0 (0/141)	1.8 (1/55)	0.11
Group A: ≤10mm	0 (0/82)	0 (0/5)	1
Group B: 11–15mm	0 (0/45)	0 (0/14)	1
Group C: 16–20mm	0 (0/14)	2.8 (1/36)	0.53
Delayed bleeding, % (n)	0 (0/141)	1.8 (1/55)	0.11
Group A: ≤10mm	0 (0/82)	0 (0/5)	1
Group B: 11–15mm	0 (0/45)	0 (0/14)	1
Group C: 16–20mm	0 (0/14)	2.8 (1/36)	0.53
Esophageal stricture, % (n)	0.7 (1/141)	0 (0/55)	0.53
Group A: ≤10mm	0 (0/82)	0 (0/5)	1
Group B: 11–15mm	0 (0/45)	0 (0/14)	1
Group C: 16–20mm	7.1 (1/14)	0 (0/36)	0.11

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

Figure

Figure 1.



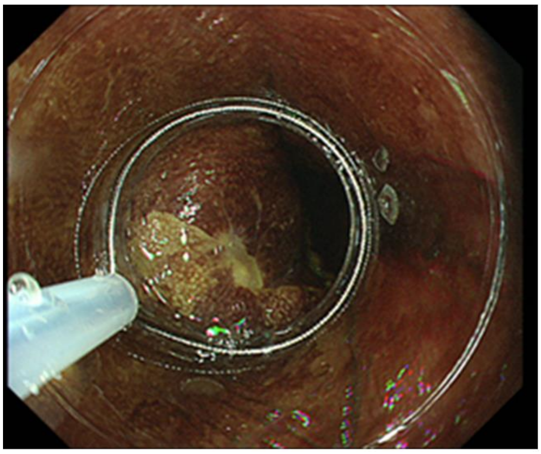
Patient flowchart

Patients flow chart of the study. SESCC: superficial esophageal squamous cell carcinoma

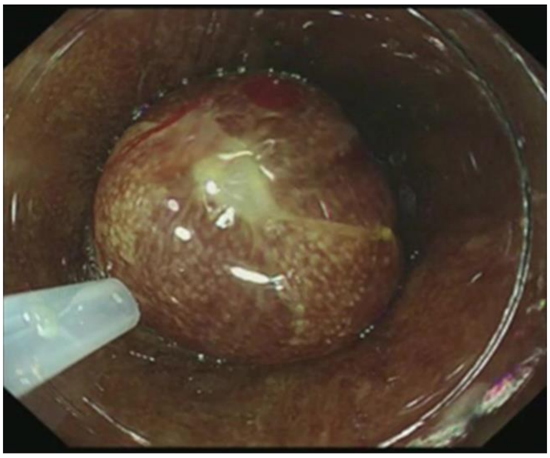
Figure 2.

a)

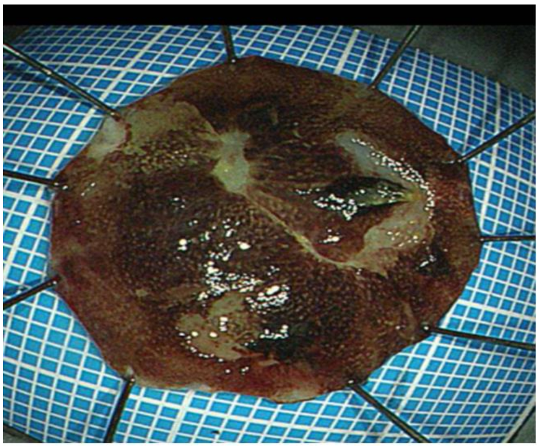
b)



c)



d)



Endoscopic mucosal resection (EMR) strategy fo superficial esophageal squamous cell carcinoma

a) Chromoendoscopy with iodine staining clearly visualized and the lesion was 15mm in size.

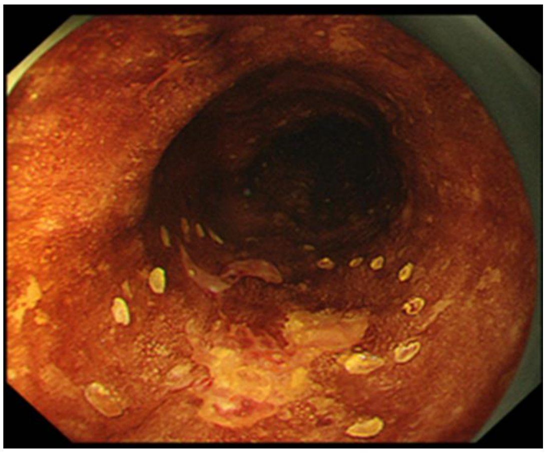
b) The snare was opened in the oblique transparent cap with an internal circumferential ridge.

c) The lesion was suctioned into the cap, and then captured and resected by the snare.

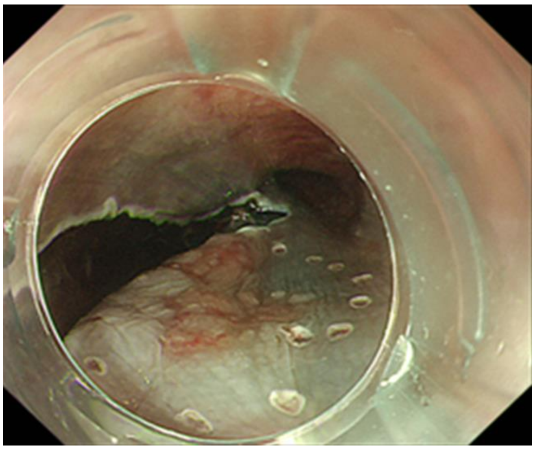
d) Resected specimen of the lesion in en bloc fashion by cap-assisted EMR.

Figure 3.

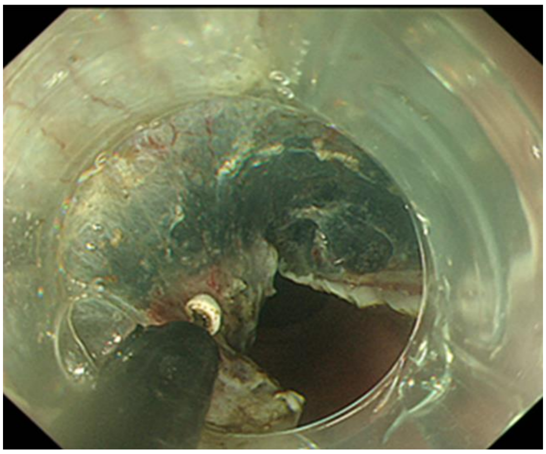
a)



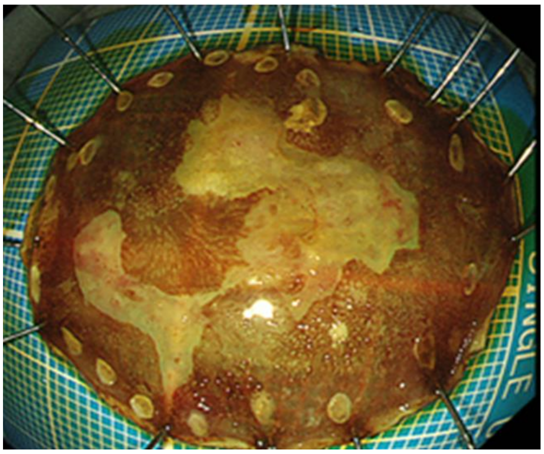
b)



c)



d)



Endoscopic submucosal dissection (ESD) strategy fo superficial esophageal squamous cell carcinoma

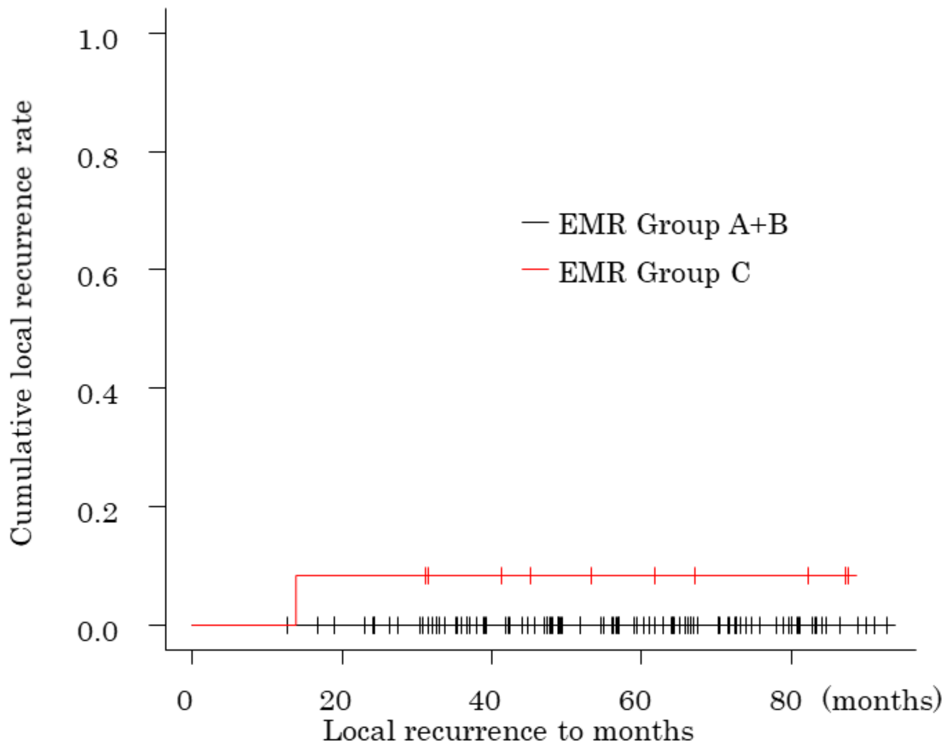
a) Chromoendoscopy with iodine staining clearly visualized and the lesion was 20mm in size.

b) Mucosal incision at the proximal and distal sides and a communication between both sides were made.

c) The endoscope entered the submucosal layer from the proximal side, and dissected submucosa with IT knife nano.

d) Resected specimen of the lesion in en bloc fashion by ESD.

Figure 4.



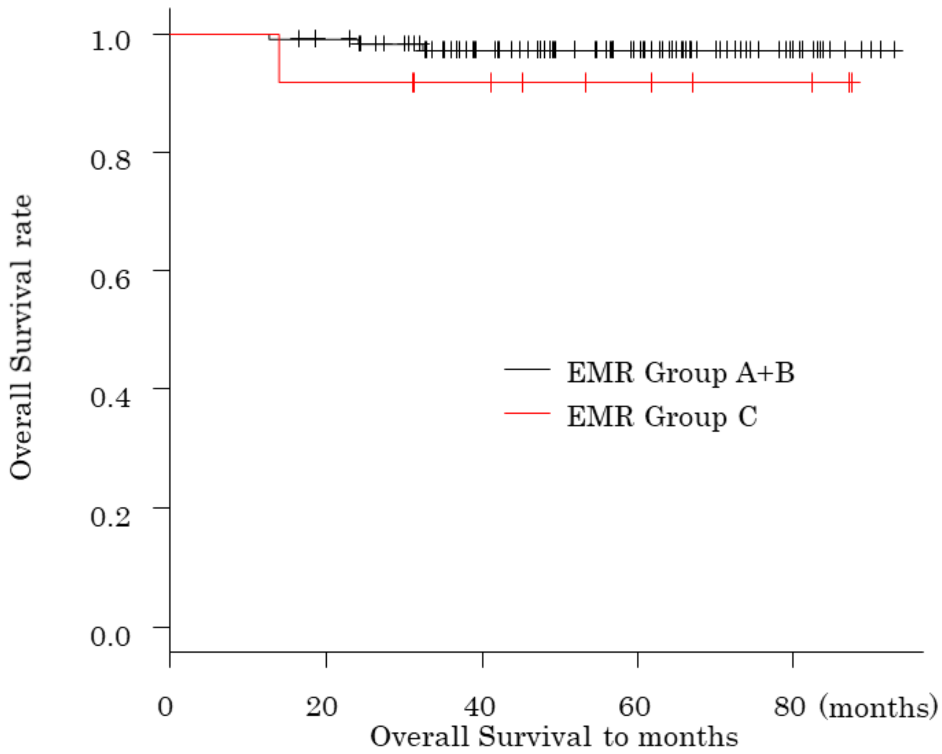
Number at risk

EMR Group A+B	108	104	80	50	15
EMR Group C	12	11	9	6	4

Cumulative incidence of local recurrence in 160 patients followed over 1 year

The cumulative local recurrence curves for superficial esophageal squamous cell carcinoma lesions with ≤15mm (Group A+B) and lesions with 16-20mm (Group C). The 5-year cumulative local recurrence rate of Group C had a significantly higher than that of Group A+B ($p < 0.01$).

Figure 5.



Number at risk

EMR Group A+B	108	104	80	50	15
EMR Group C	12	11	9	6	4

Kaplan-Meier curve of the overall survival rate in 160 patients followed over 1 year

The 5-year overall survival(OS) curves for superficial esophageal squamous cell carcinoma lesions ≤15mm (Group A+B) and lesions with 16-20mm (Group C). The 5-year OS rates were not significant differences between Group A+B and Group C ($p=0.32$).