Endoscopic Submucosal Dissection for Superficial Esophageal Neoplasms

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Abstract: *Background and Aim*: There has been a marked increase in the number of esophageal squamous cell neoplasms (SCNs) which are applicable to local treatment by virtue of recent developments in endoscopy. Endoscopic submucosal dissection (ESD) is an effective treatment for early noninvasive gastrointestinal cancers.

Aim of this study was to evaluate efficacy of ESD for superficial esophageal squamous cell neoplasms.

Subjects & Methods: Between November 2010 and March 2012, seventy-two lesions with superficial esophageal squamous cell neoplasms, which were treated by ESD in Kumamoto University Hospital, were analyzed in this study. Therapeutic efficacy, complications, and follow-up results were assessed.

Results: Mean size of the lesions was 19±14 mm (range; 1-80 mm); and mean size of the resection specimens was 29±13 mm (range; 7- 80mm). Extensive lesions over 2/3 of the circumference were observed in 17 patients. En bloc resection rate was 100% (72/72), and en block resection rate with tumor-free lateral/basal margins was 95.8% (69/72). Perforation didn't occur. Endoscopic dilation was performed for post-operative stenosis in 10 patients. In 3 patients who developed pinhole-like stenosis followed by circumferential ESD, combination treatment of oral steroid administration with endoscopic dilation could achieve favorable courses. None of the patients developed local recurrence or distant metastasis in the follow-up period.

Conclusion: ESD is a minimally invasive, relatively safe treatment method for esophageal SCNs. In particular, it is suggested that ESD combined with oral steroid administration and endoscopic dilation, might be applicable to the patients with circumferential SCNs where post-operative stenosis must follow circumferential ESD.

Keywords: Endoscopic Submucosal Dissection (ESD), Superficial Esophageal Neoplasm (SCN), Narrow-band imaging (NBI), Steroid administration, Endoscopic ultrasonography (EUS).

INTRODUCTION

There has been a marked increase in the number of esophageal squamous cell neoplasms (SCNs) indicated for local treatment by virtue of recent developments in endoscopy, including magnifying endoscopy using narrow-band imaging (NBI) and iodine staining [1-4]. Muto *et al*. reported that the detection rate of superficial esophageal carcinoma by NBI was significantly higher than that by conventional endoscopic white-light imaging (97 vs. 55%, respectively, $p < 0.001$) [4].

Noninvasive carcinoma (carcinoma in situ, EP) and intramucosal invasive carcinoma limited to the lamina propria mucosae (LPM) without vessel infiltration, have been proven to be associated with no lymph node or distant metastases [5-9].

A large number of retrospective histopathological analyses of surgically-resected esophageal SCNs have indicated that endoscopic treatment might be applicable for these lesions. In this regard, endoscopic mucosal resection (EMR) has been accepted widely for localized SCNs as an alternative to surgical treatment, especially in Japan, because of high rates of surgical mortality and postsurgical complications related to esophagectomy (range: 2.1 to 13.7%), associated with poor quality-of-life [10-12]. EMR for esophageal squamous cell carcinoma have a similar efficacy on long-term outcomes, compared with surgical treatment for early-stage neoplasms [13, 14]. However, EMR is hampered by some technical limitations; less than half of the patients treated with EMR have been reported to have an en bloc resection, and, in particular, en bloc resection of lesions larger than 20mm is extremely difficult. The residual tumor/recurrence rate after piecemeal resection has been reported as about 10-20% [15, 16]. To overcome these limitations, endoscopic mucosal dissection (ESD) has been developed to achieve an en bloc resection regardless of the tumor size. On the other hand, ESD may be associated with technical difficulty and a higher incidence of complications. Although ESD is widely

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accepted as a more reliable therapeutic procedure for large superficial gastric cancer in Japan, few studies have elucidated technical feasibility of this procedure in the esophagus.

This study was attempted to evaluate efficacy, safety and short-term follow-up outcomes of ESD for esophageal SCNs.

SUBJECTS AND METHODS

Seventy-two lesions in 63 patients treated with esophageal ESD at our hospital between November 2010 and March 2012 were retrospectively analyzed. For pre-operative diagnosis, magnifying NBI observation, iodine spray, and biopsy were performed. Endoscopic ultrasonography (EUS) was also applied for the lesions which were suspected to be with sub-mucosal invasion. All the 63 patients were confirmed to have no lymph-node metastasis by CT before the treatment. Fifty-nine SCNs, preoperatively diagnosed as high-grade intraepithelial neoplasm (noninvasive carcinoma; EP) or intramucosal invasive carcinoma (LPM), were primarily applied for ESD. Although majority of the lesions were LPM or superficial infiltrations in 11 SCNs, a small portion of these lesions were suspected MM (invasive to the muscularis mucosae) or SM1 (less than 200μm below the muscularis mucosae) infiltration. Because the patients strongly requested ESD and we need to avoid risks associated with esophagectomy /chemoradiotherapy (CRT) due to the presence of complications, ESD was performed in these eleven cases. In the remaining 2 lesions, EUS and NBI-magnified findings indicated SM2 infiltration (more than 200 μm below the muscularis mucosae). These lesions had already undergone CRT for these lesions, and difficulty in endoscopic resection was expected because of the local recurrent lesions due to fibrosis. However, ESD was applied to these cases on the patients' strong request. Written informed consent was obtained from all the patients.

Endoscopic Operating System

ESD procedures were performed by using video endoscopes (GIF-Q260J; Olympus Optical Co, Ltd, Tokyo, Japan).

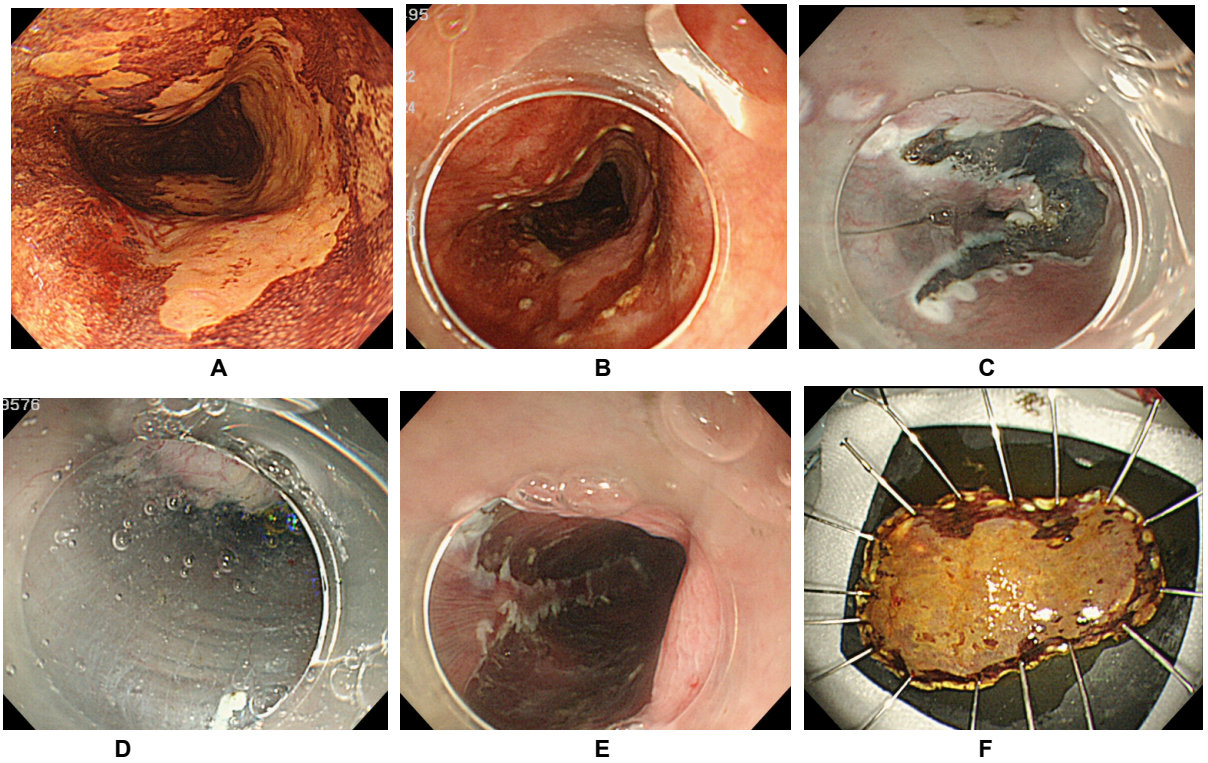

Figure 1: A representative case of ESD for esophageal neoplasm.
A: Chromoendoscopy with iodine staining to demarcate the lesion from the non-neoplastic area.
B: Marking placement around the lesion.
C: Initial mucosal incision after submucosal injection at the distal margin of the lesions.
D: Mucosal incision after submucosal injection at proximal margin of the lesion and subsequent submucosal dissection from the proximal end
E: Mucosal defect after ESD.
F: Resected specimen.

Procedure of ESD

In this study, two expert endoscopists with more than 10 years of experience performed ESD for 72 lesions in 63 patients.

After extent of lateral infiltration of the lesion is evaluated closely employing ordinary and special endoscopic techniques such as narrow band imaging and iodine staining, the resection line is determined. Marking dots were made with the Flush knife (KD-2618 JN-15; Fujinon) 2 to 3 mm outside the margins of the lesion. After sodium thiosulphate spray, a small volume of saline was injected into the sub-mucosal layer to confirm the marking, followed by sodium hyaluronate solution injection to appropriately elevate the mucosa. By mixing a small amount of dye, the injected area with sodium hyaluronate can be distinguished easily from the non-injected area even after the pre-injection of saline.

A mucosal incision around the tumor was then made with either a flash knife. The knife was gently pressed onto the mucosa. Distal half of the mucosal incision was completed first, followed by the proximal half. A hood, 4 mm in length attached at the endoscope tip, was also helpful for the safety of mucosal incision by blocking unintentional movements of the esophageal wall toward the knife. Before incising the entire circumference of the lesion, dissection of the sub-mucosa was started from the area in which the mucosal incision was completed, prior to the flattening of the lifted area as the procedure progressed. Principal knife used for the sub-mucosal dissection was the same one as that used for the mucosal incision. A representative case is shown in Figure **1**.

Statistics

Some variables in this study were described as mean (SD). All statistical analyses were performed by using SAS version 8.0 (SAS Institute Inc, Cary, NC).

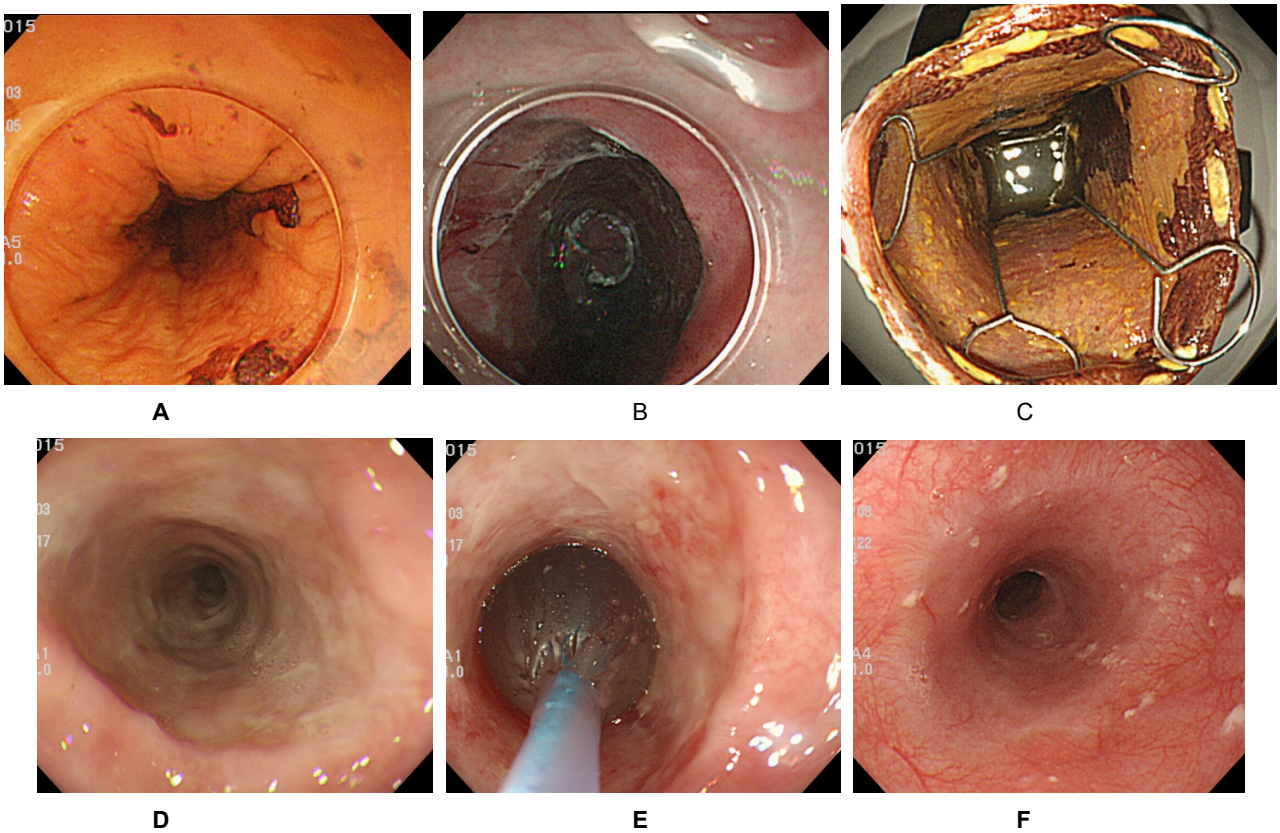

Figure 2: Clinical course of the patient (case 3) after circumferential esophageal ESD and oral steroid administration.
A: Chromo-endoscopy with iodine staining.
B: Mucosal defect after circumferential esophageal ESD.
C: Resected specimen.
D: Endoscopic findings 8 days after ESD. The esophageal lumen was so strictured that a GIF-Q260 could not be passed.
E: The stenosis was dilated to 15 mm using a balloon catheter (just once).
F: Endoscopic findings 2 months after ESD. No stenosis was observed, and the GIF-Q260 could be passed easily.

RESULTS

Background of the patients treated with esophageal ESD is shown in Table **1**. The age (mean±SD) was 67.7±8.2years, and the male-to-female ratio was 8:1.

Table1: Characteristics of 63 Patients who Underwent ESD for Superficial Esophageal SCNs

Sex, no.(%)	
Male	56(88.9%)
Female	7(11.1%)
Age, year mean±SD(range)	66.7±8.2(53-88)

The clinic-pathologic characteristics of the patients are shown in Table **2**. The macroscopic classification was as follows; IIa in 2 (2.8%) lesions, IIb in 19 (26.4%), IIc in 48 (66.7%), IIc+IIa in 2 (2.8%) and IIa+IIc in the remaining 1 (1.4%) lesions. Mean size ± SD of the lesions was 19 ± 12 mm (range 1-80 mm); mean size ± SD of the resection specimens was 29 ± 13 mm (range 7-80 mm). Seventy-one lesions (98.6%) were located in the thoracic esophagus. Sixty lesions (83.3%) (4 dysplasia, 17 EP, and 39 LPM) were considered node-negative tumors by histo-pathological evaluations of the resected specimens. All the lesions were resected in an en bloc fashion. En bloc resection with tumor free lateral/basal margins was accomplished in 69 of the 72 dissected lesions (95.8%). Three lesions presented with incomplete (R1 lateral) resection, and 2 lesions presented with incomplete (R1 basal) resection.

From the point of histological depth, 4 lesions were diagnosed as dysplasia, 17 lesions as EP, 39 lesions as LPM, 6 lesions as MM, one lesion as SM1, 5 lesions as SM2 (more than 200μm below the muscularis mucosae). R1 basal resection was performed for 2 out of the 5 lesions with SM2 invasion.

We performed ESD under conscious sedation. Mean procedure time of ESD was 62 ± 40 min (range 5-180 min). Procedural complications accompanying ESD are shown in Table **2**. Perforation didn't occur and no significant hemorrhage requiring postoperative hemostasis or blood transfusion occurred.

Extensive lesions involving more than 2/3 of the circumference were found in 17 patients (23.6%), and 3 of those had circumferential lesions. Nine of these 17 patients (53%) required endoscopic balloon dilatation (EBD) for post-ESD stenosis. None of the patients with lesions involving less than 2/3 of the circumference developed post-ESD severe stenosis that require EBD.

Table 2: Clicicopathologic Characteristic of Esophageal SCNs

Location, no. (%)	
Cervical	0(0%)
Upper thoracic	3(4.2%)
Middle thoracic	52(72.2%)
Lower thoracic	16(22.2%)
Abdominal	1(1.4%)
En block resection rate, no.(%)	72(100%)
Tumor-free lateral/basal margin (R0) rate, no. (%)	69(95.8%)
Imcoplete lateral margin (R1 lateral) rate, no. (%)	3(4.2%)
Imcoplete lateral margin (R1 basal) rate, no. (%)	2(2.8%)
Tumor size, mm, mean±SD (range)	19±14mm(1-80)
Speacimen size, mm mean±SD (range)	29±13mm(7-80)
Macroscopic classification, no. (%)	
0-IIa	2(2.8%)
0-IIb	19(26.4%
0-IIc	48(66.7%)
0-IIc+IIa	2(2.8%)
0-IIa+IIc	1(1.4%)
Preoperative determining depth of invasion of SCNs,no.(%)	
EP	31(43%)
LPM	28(38.9%)
MM	7(9.7%)
SM1	4(5.6%)
SM2	2(2.8%)
Histological depth of invasion of SCNs, no.(%)	
Dysplasia	4(5.6%)
EP	17(23.6%)
LPM	39(54.2%)
MM	6(8.3%)
SM1	1(1.4%)
SM2	5(6.9%)
Lymphovascular infiltration, no.(%)	5(6.9%)
Circumference of esophageal lumen, no.(%)	
<2/3	55(76.4%)
>2/3	17(23.6%)
<2/3, EBD(+), no.(%)	0(0%)
>2/3, EBD(+), no.(%)	9(52.9%)
Procedure time, mm. mean±SD(range)	62±40(5-180)
Local recurrence, no.(%)	0(0%)
Complication (perforation), no.(%)	0(0%)

Table **3** shows the clinic-pathological characteristics of the 3 patients who underwent circumferential esophageal ESD. Number of endoscopic dilatation performed after oral steroid administration to prevent post-ESD stenosis, was 0, 1, and 5 times, respectively.

Table 3: Clinicopathological Characteristics of 3 Patients who Underwent Circumferential Esophageal ESD

	Patients age(y)/sex	Esophageal site	Length	Preoperative determining depth of invasion of SCNs	Histological depth of invasion of SCNs	Oral steroid administration	Number of EBD sessions
1	56/M	Middle	54nm	MM	LPM	(+)	5
2	56/M	Middle	72mm	EP	EP	(+)	0
3	61/M	Lower	80mm	LPM	LPM	(+)	1

Twelve lesions in the 12 patients were considered to have concomitant risks of nodal metastases; 7 lesions in 7 patients included 6 with cancer infiltration in the muscularis (MM), one with SM1 carcinoma which increased the possibility of nodal metastasis. These lesions were closely followed up without additional treatment, at the patients' decision. In addition, lympho-vascular invasion was observed in all 5 patients with SM2 lesions, and 4 and 1 of them underwent additional surgery or chemo-radiotherapy, respectively. Two of the 3 patients with basal margin-positive lesions had SM2 lesions with a positive lateral margin, and underwent additional surgery. The remaining one patient had a lesion in contact with a scar left after ESD, and the scar was so severe that a submucosal injection failed to lift the mucosa, making it impossible to completely resect the area immediately adjacent to the scar. Therefore, the patient intentionally underwent partial resection of the tumor, followed by argon plasma coagulation (APC) of the residual carcinoma.

None of the patients developed local recurrence or distant metastasis in the follow-up period (7.1±4.4 months).

DISCUSSION

The important points for endoscopic resection for superficial esophageal SCNs are ensuring safety and achieving cure. Although surgical resection has been performed as curative treatment for early-stage esophageal cancer, 2% mortality after surgery and 40% incidence of accidental complications have been reported, indicating problems of safety in surgical resection [10-12]. In contrast, the risk of endoscopic resection is low with regard to the mortality and incidence of procedural accidents, which is promoting the spread of EMR.

EMR is less invasive and safer than conventional surgery, but complications after EMR, such as perforation, have been reported to occur in about 2-6% of patients [17-19]. On the other hand, ESD of the esophagus is more difficult than that of the stomach, and the frequency of esophageal perforation has been reported to be about 3.7-6.9% [18, 20]. Also, infections associated with perforation (mediastinitis, etc.) may follow a serious course and are occasionally lethal. Since the esophageal wall is thin and has no serosa, air leak may occur simply by exposure of the muscle layer without clear perforation, leading to mediastinal or subcutaneous emphysema. In our study, no patient died of ESD, and perforation didn't occur. None of the patients developed perforation or associated complications, probably because the two operators were highly trained and experienced in endoscopy, and tried to perform a mucosal incision and submucosal dissection after locally injecting a sufficient amount of sodium hyaluronate solution into the submucosal layer.

The only postoperative complication was benign stricture of the esophagus that could be treated with EBD. Our findings, thus, describe that ESD is a greatly safe treatment for superficial esophageal SCNs.

Extensive lesions involving more than 2/3 of the circumference were found in 17 patients (23.6%) in this study. In Japan, such lesions are considered to be relative indications for endoscopic treatment, because they often require repeated, long-term EBD. In this study, 9 (53%) of the 17 patients with such lesions required EBD.

It has been reported that usefulness of oral prednisolone administration for the prevention of stricture after circumferential esophageal ESD. Isomoto *et al*. described that the prednisolone-treated group required a significantly lower mean number of prophylactic EBD sessions (3.3 sessions) resulting in a favorable clinical course than the non-prednisolone - treated group who required a mean of 32.7 EBD sessions [21].

Also, in our study, 3 patients,who underwent circumferential ESD and received oral prednisolone, exhibited a favorable clinical course after a mean

number of 2 (0-5) prophylactic EBD sessions. Therefore, if the prevention method of post-ESD esophageal stricture would be established, it will be possible to relax the restriction on the size of superficial esophageal SCNs for ESD. Further analysis is needed.

Risk of residual tumor/relapse would be increased after EMR, when the lesions are 2 cm or more in diameter. In these lesions, residual tumor/relapse is associated with the number of the resected sections, and not with the size or circumference [15-17]. In contrast, there is no technical limitation for ESD, and resection can be performed with confirming the boundary of the lesion, suggesting that the risk of residual tumor and local recurrence might be low. In our data, the rate of en-bloc resection was 100%, suggesting that ESD could overcome the risk of residual tumor/relapse associated with EMR. Although the follow-up duration is not enough, the present study describes that no patient with esophageal SCNs meeting the criteria of node-negative tumors, has so far exhibited recurrence extraluminally after ESD. Continued long-term follow-up is needed.

In conclusion, our study suggested that ESD might be a successful and relatively safe treatment for esophageal SCNs, fulfilling the criteria of node-negative tumors. ESD should be considered as the first-line treatment in all large lesions amenable to endoscopic treatment.

However, ESD is not such a simple procedure that any one can perform easily, and complications may lead to a fatal outcome in patients. Therefore, endoscopists who are very experienced in endoscopic procedures should perform esophageal ESD after obtaining experience in gastric ESD, which can be performed relatively safely.

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