Outcomes of endoscopic submucosal dissection for superficial esophageal squamous neoplasms: a multicenter North American experience

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Background and Aims: Endoscopic submucosal dissection (ESD) is recommended as the standard of care for treating superficial esophageal squamous neoplasms (ESNs). However, the data in the Western world are limited. This study aims to describe the outcomes of ESD for ESN in North America.

Methods: We conducted a multicenter retrospective analysis of patients who underwent ESD for superficial ESN at 13 North American academic centers. The primary outcomes were the rates of en bloc, R0, and curative resection. Patient demographics, technical outcomes, clinical outcomes, and adverse events (AEs) were also reported.

Results: A total of 150 patients (39% female, mean age 70 ± 10 years) underwent ESD to treat superficial ESN with an average tumor size of 36.6 ± 27.0 mm. En bloc resection rates for all, low-grade dysplasia (LGD)/high-grade dysplasia (HGD), M1/M2, and M3/submucosal (SM)1 lesions were 97%, 97%, 100%, and 94%, respectively. R0 resection rates for all, LGD/HGD, M1/M2, and M3/SM1 lesions were 73%, 84%, 89%, and 70%, respectively. Curative resection rates for all, LGD/HGD, M1/M2, and M3/SM1 lesions were 55%, 84%, 86%, and 61%, respectively. AEs were observed in 25 patients (16.6%). The median follow-up time was 15.7 months (IQR, 6.1-28.0). Local recurrence occurred in 12 (8.0%) cases, 3 (2%) cases from curative resection, and 9 (6%) cases in noncurative resection ($P = .04$). Metastasis occurred in 8 (5.3%) of all included cases and was only evident in noncurative resections. During this period, 21 (14.0%) patients died of non-esophageal squamous cell carcinoma (ESCC)–related causes, and 7 (4.7%) patients died of ESCC.

Conclusions: ESD is a safe and effective treatment for superficial ESN with a low recurrence rate in lesions that meet the standard criteria for curative resection. (Gastrointest Endosc 2026;104:21-9.)

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INTRODUCTION

Esophageal cancer (EC) is the sixth most common cause of cancer-related death globally.[1] Esophageal squamous cell carcinoma (ESCC) is the predominant subtype of EC worldwide. Age-standardized incidence rates range from 11.2 per 100,000 in Eastern Asia to 0.9 per 100,000 in North America.[2] For patients with ESCC, the 5-year survival rate is 19.8%.[3] Conversely, stage 1 ESCC is associated with a higher 5-year survival rate of 70% to 85%, emphasizing the significance of timely detection and treatment of superficial esophageal squamous neoplasms (ESNs).[3,4]

Endoscopic submucosal dissection (ESD) is a minimally invasive technique for treating superficial ESN. There are a paucity of data from European countries describing outcomes of ESD for superficial ESN, and there are currently no data from North America.[5-9] Nonetheless, ESD has been advocated by the American Gastroenterological Association and European Society of Gastrointestinal Endoscopy (ESGE) as a treatment modality for early EC or are at a higher risk of containing cancer because ESD allows for higher en bloc resection rate with lower local recurrence rate than alternative techniques, such as EMR.[10-12] Thus, ESD has become the standard of care for treating early EC.[13]

Numerous studies from Asia have provided evidence of the effectiveness and safety of ESD for superficial ESN.[14-17] However, the adoption of ESD in the Western world has been relatively recent. The studies that currently exist from Western countries are mostly from Europe and overall redemonstrate the efficacy and safety of ESD for ESN, but there remain minor differences in the outcomes than those in studies from Eastern countries.[5-9] For example, a prior meta-analysis showed a higher rate of en bloc, R0, and curative resections in Eastern studies than in Western studies.[18] This discrepancy can be attributed to a variety of factors, including prevalence of ESN, the requirement for specialized training, the increased adverse event (AE) rate, and prolonged procedure times. Moreover, variations in reimbursement systems may also influence the regional acceptance of ESD, further contributing to variation in outcomes data. There are currently no large-scale studies of ESD for superficial ESN in North America, and it is possible that the outcomes data from a North American population may differ from those in European and Asian populations. Therefore, in this study, we aim to conduct a multicenter analysis of the outcomes of ESD for superficial ESN in a North American population.

METHODS

We conducted a multicenter retrospective analysis of patients aged 18 years and older who underwent ESD for superficial ESN at 13 academic centers in North America from 2012 to 2023. The study was approved by the organizing center's institutional review board and at each local participating institution.

The data of patients who underwent ESD for superficial ESN identified and diagnosed under endoscopic visualization were extracted from the electronic medical record at each institution.

Relevant data included patient demographics, lesion size, location, prior lesion treatment, lesion macroscopic and histologic characteristics, procedure-related AEs, and follow-up outcomes. The follow-up duration was calculated from the date of index ESD to the date of data collection.

Pathologic evaluation

Histologic characteristics, tumor size, presence of lymphovascular invasion (LVI), and depth of tumor invasion were evaluated on the resected specimen. These data were collected locally at each participating institution. The depth of the tumor was classified as intraepithelial (M1), invading the lamina propria (M2), invading the muscularis mucosae (M3), submucosal invasion $\leq$200 μm (submucosal [SM]1), and depth of submucosal invasion greater than 200 μm (SM2 or greater).

Study outcomes

The primary outcome was rates of en bloc, R0, and curative resection. R0 resection was defined as an en bloc resection with negative horizontal and vertical margins. Curative resection was defined as en bloc, R0 resection of a well-to-moderately differentiated lesion without LVI in superficial mucosal tumors (M1/M2 in the standard criteria and M3/SM1 in the expanded criteria).[11] LVI is defined as the presence of cancer cells within the lymph or blood vessels.

The secondary outcomes included (1) procedure-related AEs, which were graded as per the AEs in GI endoscopy (AGREE) classification[19]; (2) rate of local recurrence, defined as endoscopic or histologic evidence of neoplasia at follow-up endoscopy; (3) lymph node and distant metastasis, which was identified with either EUS, CT, or magnetic resonance imaging; (4) death; and (5) disease-related survival during the study period.

Severe intraprocedural bleeding was defined as clinical bleeding resulting in a reduction of hemoglobin by more than 2 g/dL or requiring periprocedural blood transfusion. Delayed bleeding was defined as the occurrence of clinical bleeding accompanied by a decrease in hemoglobin levels of more than 2 g/dL or requiring blood transfusion within 14 days of the ESD procedure. A metachronous lesion was defined as a new esophageal neoplasm that appeared at a site distinct from the primary lesion, with the diagnosis made at least 12 months after the initial ESD.

TABLE 1. Patients and lesion characteristics

Patient characteristic	*N* = 150
Female *n* (%)	58 (38.7)
Mean age in y (SD)	69.8 (10)
Median ASA class (IQR)	3 (2-3)
Prior endoscopic treatment	
None (%)	123 (82.0)
EMR (%)	4 (2.7)
Ablation (RFA or APC) (%)	3 (2.0)
Prior ESD (%)	9 (6.0)
Multiple treatments (%)	3 (2.0)
Data unavailable (%)	8 (5.3)
Location of the tumor	
Cervical (%)	5 (3.3)
Upper third (%)	21 (14.0)
Middle third (%)	77 (51.3)
Lower third (%)	45 (30.0)
Spans multiple segments (%)	2 (1.3)
Mean tumor size in mm (SD)	36.6 (27.0)
Histology of the lesion*	
Low-grade dysplasia (%)	8 (5.3)
High-grade dysplasia (%)	30 (20.0)
Intramucosal cancer (%)	50 (33.3)
Invasive cancer (%)	60 (40.0)
Data unavailable (%)	2 (1.3)
Depth of invasion*	
M1 (%)	5 (3.3)
M2 (%)	31 (20.7)
M3 (%)	23 (15.3)
SM <200 μm (%)	10 (6.7)
SM >200 μm (%)	25 (16.7)
Submucosal unspecified (%)	10 (6.7)
Data unavailable (%)	7 (4.7)

APC, Argon plasma coagulation; *ASA*, American Society of Anesthesiologists; *ESD*, endoscopic submucosal dissection, *RFA*, radiofrequency ablation, *SM*, submucosal.
*Post-ESD pathology.

TABLE 2. Resection outcomes, adverse events, and mortality

Resection outcome	Number (%)
En bloc resection rate	
All lesions (%) (*N* = 150)	146 (97)
LGD and HGD (%) (*N* = 38)	37 (97)
M1/M2 (%) (*N* = 36)	36 (100)
M3/SM1 (%) (*N* = 33)	31 (94)
SM2 or greater (%) (*N* = 36)	35 (97)
R0 resection rate	
All lesions (%) (*N* = 150)	109 (73)
LGD and HGD (%) (*N* = 38)	32 (84)
M1/M2 (%) (*N* = 36)	32 (89)
M3/SM1 (%) (*N* = 33)	23 (70)
SM2 or greater (%) (*N* = 36)	16 (44)
Curative resection rate	
All lesions (%) (*N* = 150)	83 (55)
LGD and HGD (%) (*N* = 38)	32 (84)
M1/M2 (%) (*N* = 36)	31 (86)
M3/SM1 (%) (*N* = 33)	20 (61)
SM2 or greater (%) (*N* = 36)	0 (0)
Adverse events	*N* = 25
Intraprocedural perforation (%)	1 (0.7)
Severe intraprocedural bleeding (%)	1 (0.7)
Delayed perforation (%)	1 (0.7)
Delayed bleeding (%)	3 (2.0)
Stricture formation (%)	19 (12.6)
Mortality	
Cumulative mortality (%)	21 (14.0)
Disease-related mortality (%)	7 (4.7)

HGD, High-grade dysplasia; *LGD*, low-grade dysplasia; *SM*, submucosal.

Statistical analysis

Statistical analysis was performed using Microsoft Excel (Version 16.81; Redmond, Wash, USA). Continuous values are reported as median and IQR or mean and SD where appropriate. Categorical variables are reported as numbers and percentages. Comparisons were made using the χ^2 test for categorical variables and the *t* test for continuous variables. Statistical significance was determined using a *P* value of <.05. Survival analysis was performed using a Kaplan-Meier estimate.

RESULTS

Patient and lesion characteristics

A total of 150 patients (39% female) with a mean age of 70 ± 10 years underwent ESD for the treatment of superficial ESN. The average tumor size was 36.6 ± 27.0 mm. The majority of the lesions (*n* = 77, 51%) were located in the midesophagus. Nineteen (12.7%) patients had prior endoscopic treatment of their lesion (Table 1).

Before ESD, the lesions were histologically comprised of 2 (1.3%) cases of low-grade dysplasia (LGD), 43 (28.7%) cases of high-grade dysplasia (HGD), 33 (22.0%) intramucosal cancer, and 43 (28.7%) invasive cancer. After ESD, the lesions were histologically comprised of 8 (5.3%) cases of LGD, 30 (20.0%) cases of HGD, 50 (33.3%) intramucosal cancer, and 60 (40.0%) invasive cancer. Regarding lesion depth, 5 (3.3%) were classified as M1, 31 (20.7%) as

TABLE 3. Follow-up outcomes

Follow-up outcomes	Number (%)
Local recurrence (%)	
All lesions (%)	12 (8.00)
LGD/HGD (%)	1 (0.01)
M1/M2 (%)	0 (0.00)
M3/SM1 (%)	2 (0.01)
Noncurative (%)	9 (0.06)
Metastasis (LN and distant) (%)	8 (5.3)
Median follow-up time in months (IQR)	16 (6-28)
Noncurative resection	*N* = 67
Reason for noncurative resection	
Depth of invasion (SM2 or greater) (%)	43 (64.2)
Positive lateral or deep margins (%)	41 (61.2)
Positive lateral margins (%)	27 (40.3)
Positive deep margins (%)	21 (31.3)
Lymphovascular invasion (%)	24 (35.8)
Management of noncurative resection	
Endoscopic surveillance (%)	28 (41.8)
Endoscopic retreatment (%)	11 (16.4)
Surgery (%)	14 (20.9)
Chemotherapy (%)	11 (16.4)
Radiation (%)	11 (16.4)
Metastatic recurrence with noncurative ESD (%)	8 (11.9)
Metastasis detected (LN and distant)	*N* = 8
Post-ESD histopathology	
LGD/HGD (%)	1 (12.5)
M1/M2 (%)	1 (12.5)
M3/SM1 (%)	2 (25.0)
SM2 or greater (%)	4 (50.0)
Management of metastatic recurrence	
Surgery (%)	2 (25.0)
Radiation, chemotherapy, or immunotherapy (%)	3 (37.5)
Data unavailable (%)	3 (37.5)
Median time to detect metastasis, in months (IQR)	10.0 (9.6-11.3)

ESD, Endoscopic submucosal dissection, *HGD*, high-grade dysplasia; *LGD*, low-grade dysplasia; *LN*, lymph node; *SM*, submucosal.

M2, 23 (15.3%) as M3, 10 (6.7%) as SM1, and 25 (16.7%) as SM2 or deeper.

There were a total of 17 endoscopists who performed ESD and contributed data to this study. Fifteen of the endoscopists had >200 ESD cases performed, and 2 of the endoscopists had between 100 and 200 ESD cases performed.

Resection outcomes

A total of 150 lesions were successfully treated with ESD. The overall en bloc resection, R0 resection, and curative resection rates were 97%, 73%, and 55% respectively. En bloc resection rates for LGD/HGD, M1/M2, and M3/SM1 lesions were 97%, 100%, and 94%, respectively. R0 resection rates for LGD/HGD, M1/M2, and M3/SM1 lesions were 84%, 89%, and 70%, respectively. Curative resection rates for LGD/HGD, M1/M2, and M3/SM1 lesions were 84%, 86%, and 61%, respectively (Table 2). For lesions meeting the standard and expanded criteria for resection, the rates of curative resection were 82% and 75%, respectively.

A total of 67 (45%) ESD cases were noncurative. The most common reason for noncurative resection was the depth of invasion (n = 43, 64.2%), which includes lesions that invaded deeper than SM2 (n = 25, 37.3%) or had an indeterminate depth of submucosal invasion (n = 18, 26.9%), followed by positive lateral (n = 27, 40.3%) or deep (n = 21, 31.3%) margins on histologic analysis. These outcomes are further characterized in Table 3.

Procedure-related AEs

AEs were reported in 25 patients (16.6%). Among these, 2 (1.4%) experienced intraprocedural AEs. There was 1 (0.7%) case of intraprocedural perforation and 1 (0.7%) case of severe intraprocedural bleeding, both of which were managed endoscopically (the American Society for Gastrointestinal Endoscopy Lexicon Mild). Four patients (2.8%) reported delayed AEs. Delayed perforation was reported in 1 (0.7%) case and was managed using conservative methods (AGREE grade II). Delayed bleeding occurred in 3 (2.0%) cases and was treated conservatively (AGREE grade II). Stricture formation was observed in 19 (12.7%) cases and was managed through endoscopic dilation (AGREE grade III) (Table 2).

Follow-up and recurrence

The median follow-up time after ESD was 15.7 months (IQR, 6.1-28.0). For lesions that were LGD/HGD, M1/M2, and M3/SM1, the median follow-up times were 19.0, 16.4, and 14.6 months, respectively. Among the 70 cases categorized as noncurative, 28 (41.8%) were managed with endoscopic surveillance, 14 (20.9%) were referred for surgery, 11 (16.4%) received endoscopic retreatment, 11 (16.4%) received chemotherapy, and 11 (16.4%) received radiation therapy.

Throughout the follow-up period, there were 12 instances (8.0%) of local recurrence. For LGD/HGD, M1/M2, M3/SM1, and noncurative lesions, there were 1 (0.01%), 0 (0.00%), 2 (0.01%), and 9 (0.06%) instances of local recurrence, respectively. Noncurative cases accounted for 75% of these recurrences, whereas 25% occurred in curative cases.

Metastasis occurred in 8 (5.3%) cases, which all occurred in the noncurative cases. In cases classified as curative resection, there were no metastases reported. The median time to metastatic recurrence was 10 months (IQR, 9.6-11.3 months) (Table 3). Resection outcomes and recurrence statistics for all cases are summarized in Figure 1. Detailed case-level information is provided for the cases of metastatic occurrence in Supplementary Table 1.

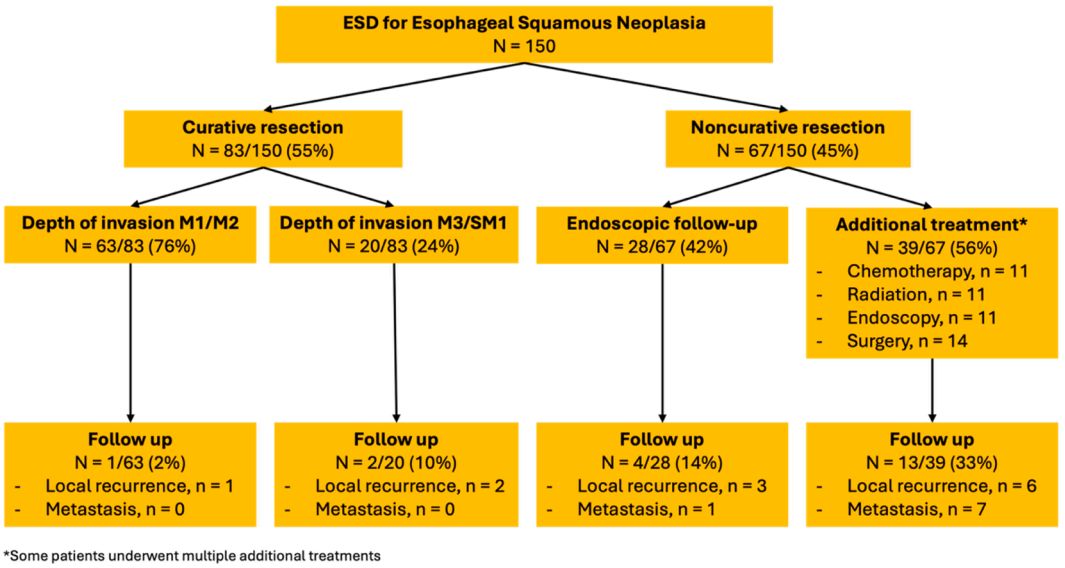


Figure 1. Diagram of resection outcomes and recurrence statistics for all endoscopic submucosal dissection (ESD) cases. *SM*, Submucosal.

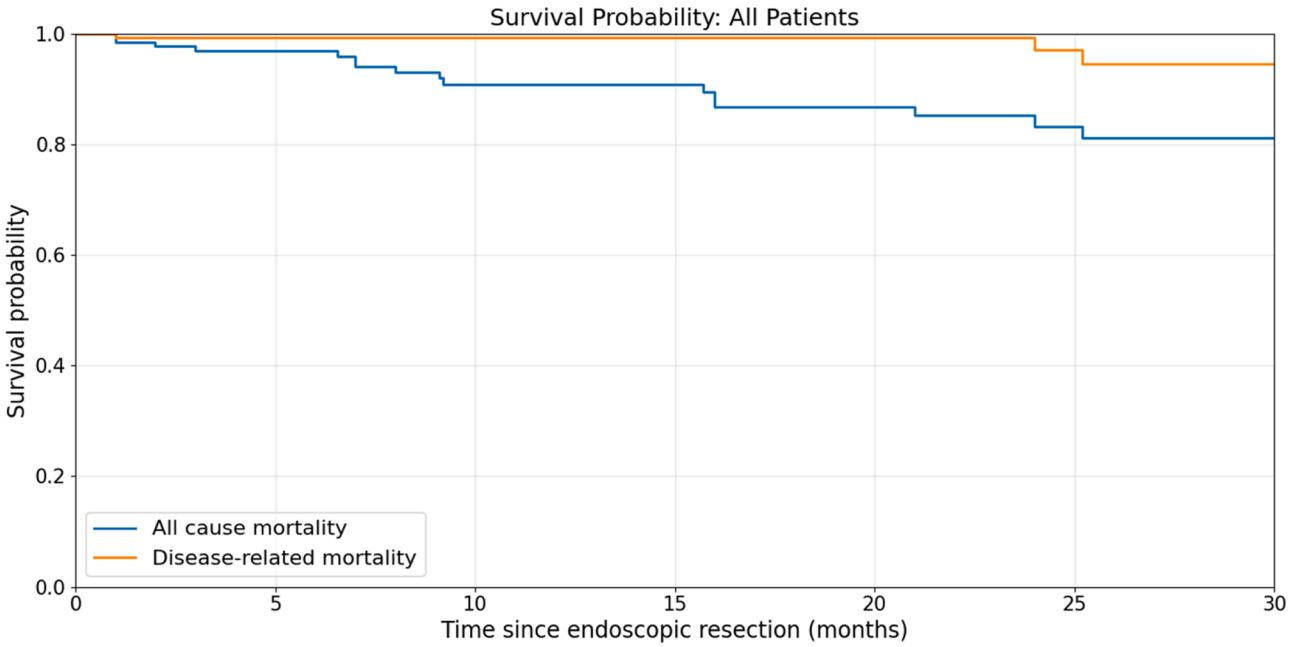
During the follow-up period, 21 (14.0%) patients died of non-ESCC-related causes, and 7 (4.7%) patients died from ESCC. Detailed case-level information is provided for the cases of disease-related mortality in Supplementary Table 2. The Kaplan-Meier survival curve for overall survival and disease-specific survival after ESD for ESCC in all cases is shown in Figure 2. The Kaplan-Meier survival curve for disease-specific survival stratified by post-ESD histopathology is shown in Figure 3. Log-rank comparison was performed between the histopathologic groups for disease-related survival and did not reveal any statistically significant difference.

DISCUSSION

ESD is recommended for treating superficial ESN according to Asian, European, and North American guidelines.[10,11,20] However, there are limited studies describing the outcomes of ESD for ESN in Western countries. Here, we conducted a multicenter study from North America of ESD for ESN that demonstrated high rates of technical success with low rates of AEs. Altogether, ESD appears to be a highly effective treatment for ESN in a Western setting.

Our study showed that the overall en bloc and R0 resection rates were as high as 97% and 73%, respectively. For LGD/HGD, M1/M2, and M3/SM1 lesions, the en bloc resection rates were 97%, 100%, and 94%, respectively. R0 resection rates were 84%, 89%, and 70%, respectively. These findings are mostly consistent with previously published reports. In a meta-analysis of 15 studies from Eastern countries, overall en bloc and R0 resection rates were 95.1% and 89.4%, respectively.[21] Multiple studies from Western countries have found similar rates of en bloc resection rates, and R0 resection rates range from approximately 81% to 90%.[5-8] The rate of R0 resection in our study is slightly lower than these other studies. When stratifying R0 resection rates by lesion depth, LGD/HGD and M1/M2 lesions have similar R0 resection rates than prior studies, but the rate of R0 resection is lower in lesions that invade M3/SM1. Our study had a higher proportion of lesions with invasion depth M3 or greater than other studies, which may account for this difference. Regardless, our study demonstrated comparable rates of en bloc resection overall compared with prior studies and comparable rates of R0 resection for lesions with invasion up to M1/M2 compared with prior European and Asian studies.

According to ESGE and Japanese guidelines, ESD is strongly recommended to treat superficial ESN limited to a depth of M1/M2, and it is weakly recommended to treat superficial ESN limited to M3/SM1.[11,20] A previous multicenter study conducted in Japan reported that cases with depth of invasion limited to M1/M2 achieved a curative resection rate of 68.9%, whereas a curative resection rate of only 12.3% was reported for cases with depth of invasion up to M3/SM1.[22] In Western studies, the rate of curative resection reported in cases with lesion depth up to M1/M2 varies from 46.2% to 71.4%[7,8] Our study revealed that the overall curative resection rate stood at just 55%, a figure lower than those reported in Asian studies. One potential reason for the low overall curative rate could be the high inclusion of M3 and submucosal lesions in the study. When focusing solely on lesions with absolute



Number at risk

	0 mo	6 mo	12 mo	18 mo	24 mo	30 mo
All cause mortality	150	106	80	62	44	33
Disease-related mortality	150	106	80	62	44	33

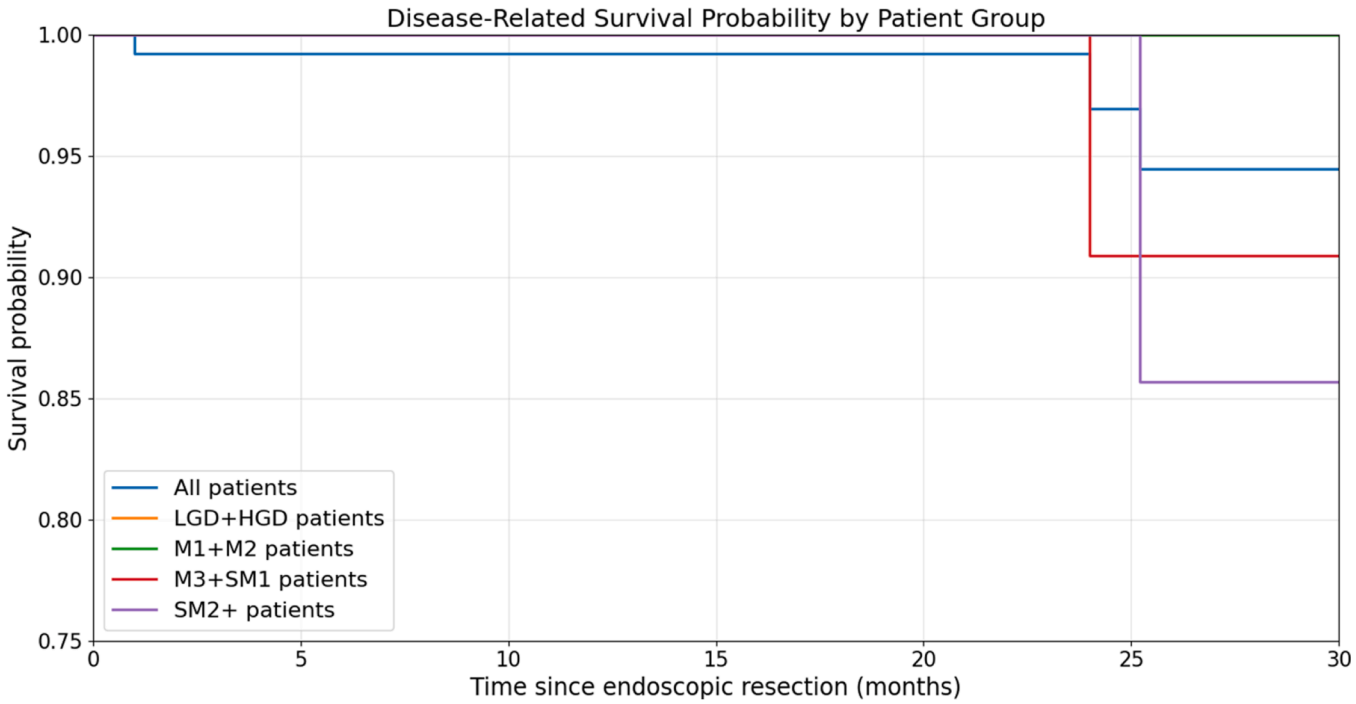
Figure 2. Kaplan-Meier survival curve for overall survival and disease-specific survival after endoscopic submucosal dissection for esophageal squamous cell carcinoma in all cases.

indications, the curative rate for LGD and HGD lesions is 82%, and for M1/M2 lesions is 83%. However, upon analyzing the curative resection rate for M3 and deeper lesions, a significant decrease to only 58% was observed. This suggests that there is room for improvement in lesion selection before performing ESD.

Moreover, 27 (18%) of the lesions in our study had previous endoscopic treatment. A prior European study reported that 91.8% of esophageal lesions that underwent ESD did not have previous endoscopic treatment, which is a higher proportion than in our study.[7] Scarring and submucosal fibrosis from prior intervention may also contribute to the increased technical difficulty of the ESD procedure. In addition, the elevated success rate in the Asian study could potentially be attributed to the endoscopists' familiarity with the procedures. Eastern countries have been performing ESD for many years before its adoption in Western countries, so the higher curative resection rate may reflect the endoscopists' technical skill and familiarity with the procedure.

Regarding AEs, we found intraprocedural AEs occurred in 1.4% of cases, and delayed AEs (excluding stricture formation) occurred in 2.8% of cases. The low rate of intraprocedural AEs is similar compared with other studies, which show rates of intraprocedural AEs ranging from approximately 0% to 9%.[5,8] Similarly, we showed comparable rates of delayed AEs, compared with another study, which showed a 1.9% rate of delayed perforation and 2.6% rate of delayed bleeding.[7] Stricture formation occurred in 12.7% of cases, and all were managed with endoscopic dilation. Rates of stricture formation range from about 5% to 20% in other Western studies, which is in alignment with our findings.[5-8] Overall, these results confirm that ESD is a relatively safe treatment for superficial ESN.

In our study, cases with curative resection had a 3.8% rate of local recurrence and a 0% rate of metastatic recurrence. Noncurative cases had a 12.9% rate of local recurrence and an 11.9% rate of metastatic recurrence. A European study showed a 0% rate of local recurrence and a 2.6% rate of metastatic recurrence in curative ESD cases.[5] A Japanese study showed a 4.3% rate of metastatic recurrence in curative ESD versus a 23.6% rate of metastatic recurrence in noncurative ESD.[15] Although there are variations in the reported numbers, it is apparent in all studies that the curative group consistently exhibits lower rates of local



Number at risk

	0 mo	6 mo	12 mo	18 mo	24 mo	30 mo
All patients	150	106	80	62	44	33
LGD+HGD patients	38	29	25	19	14	8
M1+M2 patients	36	28	21	17	12	10
M3+SM1 patients	33	22	17	15	11	10
SM2+ patients	25	19	13	10	8	7

Figure 3. Kaplan-Meier survival curve for disease-specific survival stratified by histopathology. *HGD*, High-grade dysplasia; *LGD*, low-grade dysplasia; *SM*, submucosal.

recurrence and metastasis. This again underscores the significance of achieving a high curative resection.

Management of noncurative resections is typically accomplished with endoscopic surveillance, additional surgical intervention, or adjuvant therapies. In this study, the largest proportion (41.8%) of noncurative cases underwent endoscopic surveillance or retreatment, whereas 16.4% received chemotherapy, 16.4% received radiation, 16.4% received endoscopic retreatment, and 20.9% underwent surgery. This contrasts with a previous study conducted in Europe, where 43% of cases received surgery, 35% underwent endoscopic surveillance, and 20% received chemoradiation.[5] It is possible that more aggressive management after noncurative ESD may be required to improve outcomes, such as decreasing the rates of local and metastatic recurrence.

Regarding mortality outcomes, a total of 7 (4.7%) patients died of ESCC. All the patients who died of ESCC had a noncurative resection. The post-ESD pathology for many of these patients was invasive cancer that underwent subsequent surgery or retreatment if offered, which may indicate that these patients were not appropriate candidates for ESD. Furthermore, post-ESD management for some of these patients was insufficient, as surgery was not offered because these patients were not surgical candidates. The mortality results in our study are aligned with a previous German study, which reported no ESCC-related death after curative resection. The ESCC-related deaths observed in the German study were primarily within the muscularis mucosae and submucosa/LVI patient groups.[5] However, a notable disparity emerged in terms of overall mortality rates. The German study reported significantly higher all-cause and disease-related mortality rates than the current analysis (29/58 [50%] and 5/58 [8.6%], respectively). This discrepancy may be attributed to differences in patient demographics between the studies, as well as to the extended

follow-up period of 3.9 years in the German study as opposed to the 16-month duration in our investigation.[5]

Although our study provides a comprehensive analysis of esophageal ESD as a therapy for ESN in a North American population, it is important to acknowledge the limitations of this research. First is the retrospective nature of the study. It is possible that some information or AEs following the procedure may not have been accurately recorded or could be underreported. Second, this study provides medium-term follow-up data (16 months). Prior research has demonstrated that local and metastatic recurrence after ESD for ESCC occurs at an average of 19 months after the initial endoscopic resection.[23] Thus, our study may underestimate the rate of recurrence and metastasis. Finally, there is currently a lack of standardized surveillance for ESCC after ESD procedures across different medical centers, which could potentially lead to varied rates of recurrence. Future prospective studies with longer follow-up times and standardized follow-up procedures and durations will better characterize the long-term results of ESD for ESN.

In conclusion, the ESD procedure is a safe and feasible treatment of patients with superficial ESN. ESD demonstrates a high rate of complete resection with acceptable safety profiles, especially in case with an absolute indication. The risk of local recurrence and metastasis is low after curative ESD. On the basis of the study findings, we recommend continued use of ESD as a treatment option for superficial esophageal neoplasia. Further prospective studies are needed for improved characterization of long-term outcomes.

DISCLOSURE

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Abbreviations: AE, adverse event; AGREE, Adverse Events in Gastrointestinal Endoscopy (classification system); EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; ESGE, European Society of Gastrointestinal Endoscopy; ESN, esophageal squamous neoplasm; HGD, high-grade dysplasia; LGD, low-grade dysplasia; LVI, lymphovascular invasion; SM, submucosal (depth classification: SM1, SM2, etc; M1, M2, M3, depth classifications of tumor invasion into mucosal layers).

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SUPPLEMENTARY TABLE 1. Cases of metastatic diseases (LN/distant)

Case	Lesion size (mm)	Histopathology	Curative resection	Post-ESD management	Time to detect metastasis (mo)	Survival time (mo)	Follow-up status
1	15	M2	No	None (patient not a surgical candidate)	72	72	Died of ESCC
2	30	SM2	No	Surgery	39	N/A	Alive
3	15	SM2	No	None (patient not a surgical candidate)	6	34	Died of ESCC
4	160	SM1	No	Surgery	12	24	Died of ESCC
5	40	SM1	No	Endoscopic retreatment	3	N/A	Alive
6	40	SM2	No	Surgery	4	16	Died of an unrelated cause
7	29	HGD	No	Surgery	4	16	Died of unrelated cause
8	50	SM2	No	Surgery	2	N/A	Alive

ESCC, Esophageal squamous cell carcinoma; *ESD*, endoscopic submucosal dissection; *HGD*, high-grade dysplasia; *LN*, lymph node; *N/A*, not applicable; *SM*, submucosal.

SUPPLEMENTARY TABLE 2. Cases of disease-related mortality

Case	Lesion size (mm)	Histopathology	Curative resection	Post-ESD management	Recurrence/metastasis/ metachronous lesion	Survival time (mo)
1	150	SM2	No	Surgery	None	1
2	160	SM1	No	Surgery, chemotherapy	Metastatic	24
3	30	SM2	No	Surgery	None	25
4	12	SM2	No	Endoscopic retreatment, surgery	Local	34
5	15	M2	No	None (patient not a surgical candidate)	Metastatic	73
6	15	SM2	No	None (patient not a surgical candidate)	Metastatic	34
7	30	M3	Yes	Endoscopic retreatment	Metachronous lesion	48

ESD, Endoscopic submucosal dissection, *SM*, submucosal.