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Article

Favorable Long-Term Outcomes of Early Esophageal Squamous Neoplasia with Muscularis Mucosa Involvement after Endoscopic Submucosal Dissection

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Abstract: Ambiguity exists over treatment and surveillance strategies after endoscopic submucosal dissection (ESD) for esophageal squamous cell neoplasia (ESCN) with unfavorable histologic features. This study investigated the long-term outcomes of ESD in high-risk ESCN patients. We retrospectively included early ESCN patients treated with ESD at two medical centers in Taiwan between August 2010 and December 2023. Demographic, endoscopic, and pathological data were collected. Among 146 patients (mean age 59.17 years) with 183 lesions, 73 (50%) had a history of head and neck cancer (HNC). En bloc and R0 resection were achieved in 100% and 95.6% of the lesions, respectively. The 5-year overall survival (OS), disease-specific survival (DSS) and local recurrence rates were 42.7%, 94.7% and 11%. R0 resection was significantly associated with recurrence in univariate analysis (adjusted OR: 0.23, 95% CI: 0.05–0.99, $P=0.05$). Alcohol abstinence was independently associated with lower recurrence (adjusted OR: 0.20, 95% CI: 0.08–0.48, $P<0.001$). Patients with pT1a-MM (muscularis mucosa invasion) had comparable OS ($P=0.82$), DSS ($P=0.617$) and recurrence ($P=0.63$) rates to those with pT1a-EP/LPM (epithelium/lamina propria invasion). The long-term outcomes of ESCN patients after ESD for expanded indications were satisfactory. ESD could be considered in selected ESCN patients involving the muscularis mucosa, notably among high-risk HNC patients.

Keywords: Esophageal squamous cell carcinoma; endoscopic submucosal dissection; second primary tumor; head and neck cancer; expanded indication

1. Introduction

Although the overall prognosis of esophageal squamous cell carcinoma (ESCC) is poor, with 5-year overall survival (OS) rates ranging from 15% to 25% [1], early esophageal squamous cell neoplasia (ESCN) is considered a curable disease [2,3]. The reported 5-year OS rate for patients diagnosed with early ESCC is approximately 80% following esophagectomy [4]. Endoscopic submucosal dissection (ESD) is an advanced endoscopic technique that was introduced to manage early gastrointestinal tract neoplasia in the 1990s. For selected patients with early ESCN, ESD has emerged as an alternative minimally invasive treatment option, with comparable outcomes to surgical esophagectomy [5]. A real-world cohort study with a 21-month follow-up of patients with early ESCN found no statistically significant differences in all-cause mortality (7.4% vs 10.9%; $P=0.209$) and rate of cancer recurrence or metastasis (9.1% vs 8.9%; $P=0.948$) between ESD and esophagectomy [6]. Moreover, the authors reported a lower risk of non-fatal severe adverse events in the patients who underwent ESD (15.2% vs 27.7%; $P=0.001$) [6].

Favorable long-term outcomes have been reported in early ESCN patients undergoing ESD, particularly when the invasion is limited to the epithelium/lamina propria/muscularis mucosa (pT1a-EP/LPM/MM) or involves the superficial submucosa limited to 200 μm (pT1b-SM1), with 5-year OS rates of 90.5% to 95.1% for pT1a-EP/LPM, 71.1% to 84.2% for pT1a-MM, and 70.8% for pT1b-SM1, respectively [7–12]. However, these data were mostly obtained from Japanese cohorts, with only a few from Western countries. Furthermore, many of these studies excluded individuals with a history of synchronous second primary cancer [7–9].

In Taiwan, the rate of synchronous second primary ESCN has been reported to range from 15.2~23.3% in head and neck cancer (HNC) patients [13,14], and worse OS has been demonstrated in HNC patients with synchronous ESCN compared to those without [15]. According to recent studies, endoscopic screening for second primary esophageal cancer in patients with oral cavity and hypopharyngeal cancer can significantly enhance early detection and decrease all-cause mortality [16,17]. Nevertheless, long-term outcome data for ESD in patients with second primary esophageal neoplasia and HNC are still insufficient [12]. Therefore, this study aimed to examine the long-term outcomes of ESD for second primary ESCN among high-risk patients, particularly focusing on expanded indications.

2. Materials and Methods

2.1. Study Design and Patient Enrollment

This retrospective cohort study enrolled patients with early ESCN treated with ESD between August 2010 and December 2023 at two medical centers in Taiwan. All patients met the inclusion criteria, which were: (1) histologically confirmed low-grade intraepithelial neoplasia, high-grade intraepithelial neoplasia (HGIN) of the esophagus, or early ESCC including pT1a-EP/LPM, pT1a-MM and pT1b-sm1/sm2; (2) absence of lymph node or distant metastases on radiological investigations; and (3) no history of prior chemo- or radiation therapy for ESCC. Long-term outcome data were collected from medical records, and any missing information was obtained through telephone conversations with the patients or their family. Alcohol abstinence is defined as having abstained from alcohol for at least one year after ESD and continuing to abstain until the last follow-up date. This study was approved by the Institutional Review Board of Far Eastern Memorial Hospital (FEMH-106090-E), and the requirement for written informed consent was waived because of the absence of identifiable information in the data analyzed.

2.2. ESD Procedure and Surveillance Methods

All enrolled patients underwent magnifying endoscopy with narrow-band imaging (ME-NBI) and optional chromoendoscopy using 2% Lugol's solution to evaluate the intraepithelial papillary capillary loops and Lugol-voiding areas [18,19]. Overnight fasting and prophylactic antibiotics were given, and the patients were placed in the supine or left decubitus position under intravenous sedation or general anesthesia. ESD with mucosal marking and incision, followed by submucosal

dissection and specimen retrieval was performed using dedicated endoknives and accessories. The resected specimens were sliced into 2 mm sections and fixed in formalin using standard methods following the Japan Esophageal Society recommendations, and all specimens were reviewed by experienced pathologists [20]. The pathological invasion depth, lymphovascular and perineural invasion, histological subtype and differentiation degree, vertical and lateral margins were evaluated.

The first follow-up endoscopy in all cases was performed at 3 to 6 months after ESD. Subsequent endoscopic surveillance was repeated every 6 months. Computed tomography (CT) was performed for follow-up in all patients with components of invasive carcinoma in resected specimens.

2.3. Definition of Outcomes

OS, disease-free survival (DFS) and disease-specific survival (DSS) were compared among patients with different invasion depths and those with or without HNC. OS was defined as the time from ESD to decease from any cause. DFS was defined as the time from ESD to esophageal cancer recurrence or death from any cause. DSS was defined as the duration from ESD to death specifically attributed to the ESCN. Complete local remission (CLR) was defined as R0 resection plus normal first follow-up endoscopy.

Local recurrence and metastatic recurrence were evaluated by endoscopy, CT and/or positron emission tomography. Local recurrence was defined as the development of ESCN at the ESD site of the primary lesion, while metastatic recurrence was defined as a relapse involving other organs or lymph nodes. Metachronous recurrence was defined as the development of an ESCN at a location different from the primary lesion site over 6 months after the index ESD. Furthermore, we also investigated potential correlations between the occurrence of any recurrence and baseline characteristics of the patients as well as lesions.

In terms of adverse events from ESD procedures, esophageal stricture was defined as narrowing of the lumen that a standard adult gastroscope could not pass or required endoscopic dilation. Post-ESD bleeding was defined as bleeding occurring after the ESD, characterized by a decrease in hemoglobin level > 2 g/dL, presence of hematemesis or melena or confirmation of bleeding through endoscopic, radiological, or surgical evidence. Esophageal perforation was defined as the presence of a visible defect in the esophageal wall exposing the mediastinal cavity.

2.4. Statistical Analysis

Basic characteristics of the patients were evaluated by descriptive statistics. Discrete data are presented as numbers and percentages, and continuous variables are expressed as mean values ($\pm$ standard deviation; SD). The chi-square test was used to evaluate categorical variables. Two-tailed P-values of < 0.05 were used to determine statistical significance. Univariate and multivariate logistic regression analyses were used to identify risk factors associated with outcomes. Variables from univariate analysis with P values < 0.10 were included in the multivariate model. Survival analysis was done using the Kaplan-Meier method along with a log-rank test to assess the statistical significance of differences in survival curves among different groups. All statistical analyses were performed with SPSS for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). The study results were reviewed by expert biostatistician Dr. Hsiu-Jung Liao.

3. Results

3.1. Patients, Endoscopic and Pathologic Characteristics

A total of 183 lesions in 146 patients were enrolled. Table 1 summarizes the demographic characteristics of the study population. The mean ($\pm$ SD) patient age was 59.17 (± 9.45) years, and 89% (130/146) of the patients were male. The study included 132 (90.4%) patients who were alcohol drinkers, 68.9% of whom abstained from alcohol prior to enrollment. A total of 73 (50%) patients had a history of HNC. Table A1 details the location and stage of HNC in this study. The endoscopic and pathological characteristics are also summarized in Table 1. Among the lesions, 43 (23.5%) extended to more than three-fourths of the circumference. The pathologic stage was low-grade intraepithelial

neoplasia in 16 (8.7%) lesions, HGIN/T1am1 in 90 (49.1%), T1am2 in 10 (5.5%), T1am3 in 42 (23%), T1bsm1 in 10 (5.5%), and T1bsm2 in 15 (8.2 %) lesions. The frequencies of lymphovascular invasion (LVI) and perineural invasion were 14/183 (7.6%) and 3/183 (1.6%), respectively.

Table 1. Clinical characteristics of 183 lesions in 146 patients.

Variable	Lesion No. (%)
Patient characteristics	
Age (mean ± SD), years	59.17 ± 9.45
Sex	
Male	130 (89)
Female	16 (11)
Smoking	125 (85.6)
Alcohol drinker	132 (90.4)
Betel nut chewing	64 (43.8)
Smoking cessation	48 (38.4)
Alcohol abstinence	91 (68.9)
Betel nut cessation	45 (70.3)
HN cancer history	73 (50)
Endoscopic characteristics	
Tumor location	
Upper third of the esophagus	24 (13.1)
Middle third of the esophagus	102 (55.7)
Lower third of the esophagus	57 (31.1)
Endoscopic tumor size (mean ± SD), cm	2.48 ± 1.90
Circumference of the tumor	
< 1/2	71 (38.8)
< 3/4	140 (76.5)
≥ 3/4	43 (23.5)
JES type	
B1	140
LGIN/HGIN/T1am1/T1am2	109 (77.9)
T1am3/ T1bsm1	28 (20)
T1bsm2	3 (2.1)
B2	43
LGIN/HGIN/T1am1/T1am2	7 (16.3)
T1am3/ T1bsm1	24 (55.8)
T1bsm2	12 (27.9)
Pathological characteristics	
Histological subtype	
Well differentiated (G1)	18 (23.3)
Moderately differentiated (G2)	55 (71.4)
Poorly differentiated (G3)	4 (5.1)

LVI	14 (7.6)
Perineural invasion	3 (1.6)
Pathologic stage	
LGIN	16 (8.7)
HGIN/T1am1	90 (49.1)
T1am2	10 (5.5)
T1am3	42 (23)
T1bsm1	10 (5.5)
T1bsm2	15 (8.2)

SD: standard deviation; HN cancer: head and neck cancer; LVI: lymphovascular invasion.

3.2. Short-Term Outcomes and ESD-Related Complications

The short-term outcomes and complications are shown in **Table 2**. En bloc, R0 resection and CLR were achieved in 183 (100%), 175 (95.6%) and 161 (88%) of the 183 lesions, respectively. Post-ESD stricture developed in 18 (9.8%) of the 146 patients, with no cases developing bleeding or perforation, and no cases of procedure-related mortality.

Table 2. Outcomes and complications of patients treated with ESD.

Variable	Lesion No. (%)
Short term outcomes	
En bloc resection, lesions No. (%)	183 (100)
R0 resection, lesions No. (%)	175 (95.6)
Complete local remission, lesions No. (%)	161 (88)
Overall post-ESD AE	18 (9.8)
Stricture	18 (9.8)
Bleeding	0
Perforation	0
Long term outcomes	
Mean follow-up period (mean ± SD), month	37.05 ± 26.79
Overall survival	
1-year	124 (91.9)
3-year	66 (67.3)
5-year	36 (48)
Disease-specific survival	
1-year	134 (99.3)
3-year	96 (98)
5-year	71 (94.7)
Recurrence	30 (20.5)
Local recurrence	16 (11.0)
Metachronous recurrence	14 (9.5)
Time to recurrence (mean ± SD), month	24.50 ± 24.31

ESD: endoscopic submucosal dissection; AE: adverse event; SD: standard deviation.

3.3. Long-Term Outcomes

The long-term outcomes are presented in Table 2. The mean ($\pm$ SD) follow-up time was 37.05 months ($\pm$ 26.79), and the 5-year OS and DSS rates were 42.7% and 94.7%, respectively. Over the 10-year follow-up period, the cumulative recurrence rate was 20.5%. Specifically, the 5-year local recurrence rate was 11%, and metachronous recurrence occurred in 14 cases (9.5%). The 5-year cumulative incidence of metastatic recurrence was 2.8% in the pT1a-EP/LPM group and 7.8% in the pT1a-MM group.

Figure 1a and 1b show that pathologic stage had statistically significant impacts on OS ($P=0.022$) and DSS ($P=0.007$). In the HGIN/pT1a-EP/LPM group, the 3-year and 5-year OS rates were 67.5% and 50%, respectively, compared to 68.8% and 52% in the pT1a-MM group ($P=0.82$, Figure 2a). Kaplan Meier curve showed no statistically significant difference in OS when comparing the HGIN/pT1a-EP/LPM group with the pT1a-MM group without LVI ($P=0.793$, Figure 2b). The 5-year DSS rates were 96.7% and 100% in the HGIN/pT1a-EP/LPM and pT1a-MM groups, respectively ($P=0.617$, Figure 2c). In the patients with pT1a-MM, the presence of LVI did not affect OS ($P=0.96$, Figure 2d). The causes of death in our study population are detailed in Table A2.

Table A3 provides the analysis of the impact of HNC on OS, DSS, and DFS. The patients with HNC had a lower 5-year OS rate than those without HNC (adjusted odds ratio [aOR]: 0.31, 95% confidence interval [CI]: 0.12-0.82, $P=0.018$). In addition, a higher DFS was also found in the patients without HNC in Kaplan-Meier curve ($P=0.013$, Figure A1). No significant difference was observed in the recurrence rate among different locations of HNC ($P=0.915$, Figure A2-A4).

The descriptive data of the patients who underwent additional therapy are shown in Table A4. Following ESD, a total of 19 patients received additional therapy, with 13 patients (68.4%) undergoing concurrent chemoradiotherapy. The primary reason for additional therapy was failure to achieve R0 resection (8 patients, 42.1%), followed by deep submucosal invasion (5 patients, 26.3%).

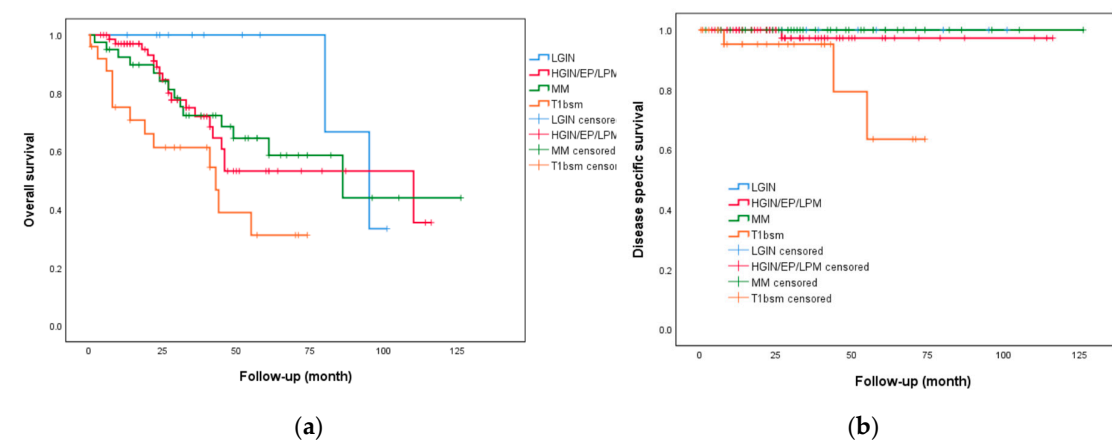


Figure 1. Kaplan-Meier curve for the impact of pathologic stage on overall survival and disease-specific survival (a) Statistically significant difference was observed ($P = 0.022$) for overall survival.; (b) Statistically significant difference was observed ($P = 0.007$) for disease-specific survival.

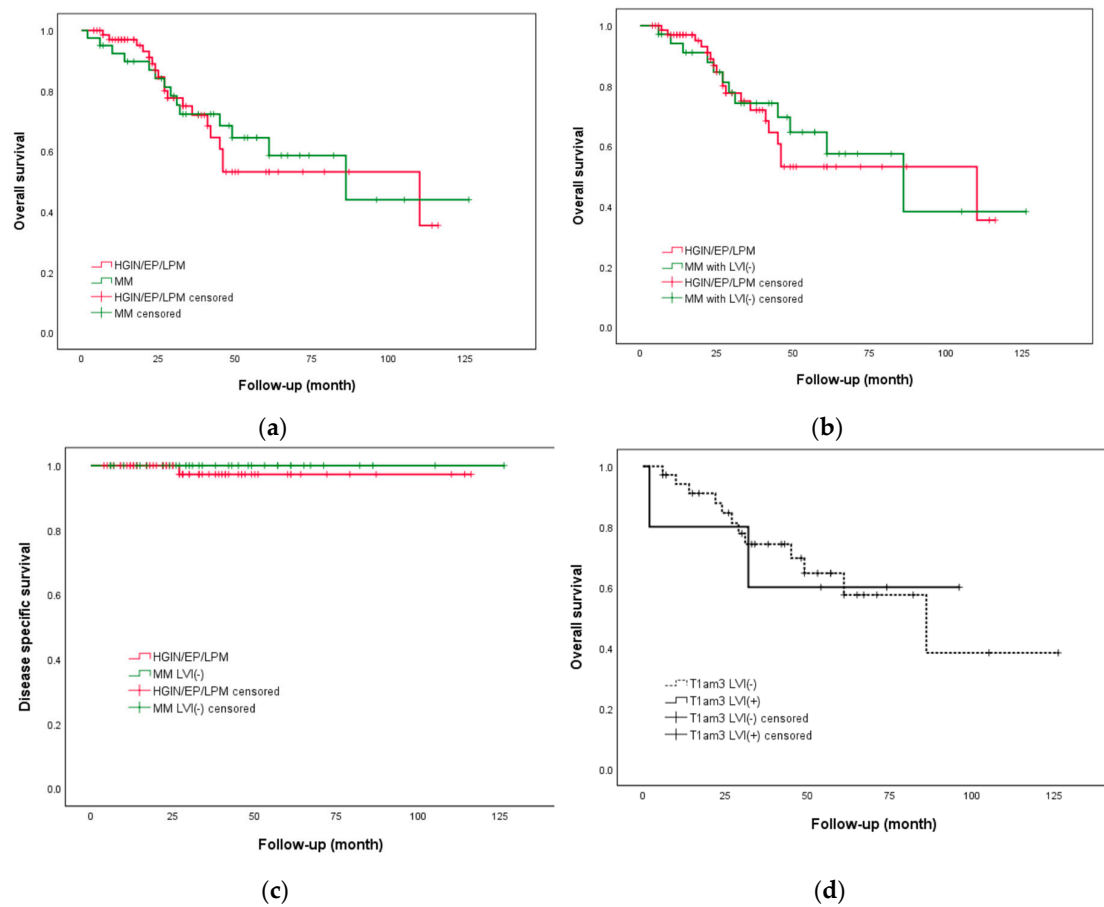


Figure 2. Kaplan meier curve of patients with HGIN/pT1a–epithelium/lamina propria mucosa (HGIN/EP/LPM) without additional therapy and patients with pT1a–muscularis mucosa (MM), LVI negative and no additional therapy (a) overall survival between patients with HGIN/EP/LPM and those with MM (P = 0.82); (b) overall survival between HGIN/EP/LPM patients and MM patients without LVI (P=0.793); (c) disease-specific survival between HGIN/EP/LPM patient and MM patients without LVI (P=0.617); (d) overall survival with respect to the presence of lymphovascular invasion (LVI) in T1am3 (pT1a–muscularis mucosa) patients (P = 0.96).

3.4. Predictors Associated with Recurrence

The results of univariate and multivariate analyses for the factors associated with recurrence after ESD are demonstrated in Table 3. The patients who achieved R0 resection and CLR, and those who abstained from alcohol consumption had a lower rate of recurrence. Multivariate analysis showed that alcohol abstinence was the only independent factor associated with a decreased recurrence rate (aOR: 0.20, 95% CI: 0.08-0.48, P<0.001). Kaplan-Meier curve demonstrated no statistically significant difference in recurrence between the patients with HGIN/pT1a–EP/LPM and those with pT1a-MM (p=0.63) (Figure 3a and 3b).

Table 3. Univariate and multivariate analysis of factors associated with recurrence.

	Recurrence (n=30)	Non- recurrence (n=116)	Univariate		Multivariate	
			P Value	OR (95% CI)	P Value	OR (95% CI)
Males	27 (90%)	103 (89%)	0.85	1.14 (0.30-4.27)		

Age (mean±SD), years	56.63±9.59	59.83±9.34	0.10	0.96 (0.92-1.01)		
Smoking	26 (87%)	99 (85%)	0.85	1.12 (0.35-3.60)		
Alcohol	30 (100%)	102 (88%)				
Betel nut	15 (50%)	49 (42%)	0.45	1.37 (0.61-3.06)		
Smoking cessation	13 (50%)	35 (35%)	0.17	1.82 (0.76-4.37)		
Alcohol abstinence	12 (40%)	79 (78%)	<0.001	0.19 (0.08-0.46)	<0.001	0.20 (0.08-0.48)
Betel nut cessation	11 (73%)	34 (69%)	0.77	1.21 (0.33-4.43)		
HN cancer	16 (53%)	57 (49%)	0.68	1.18 (0.53-2.64)		
Oral cavity cancer	3 (19%)	15 (26%)	0.57	0.67 (0.17-2.70)		
HPC and laryngeal cancer	10 (63%)	30 (53%)	0.49	1.50 (0.48-1.68)		
LVI	5 (17%)	9 (8%)	0.15	2.38 (0.73-7.71)		
Perineural invasion	0	3 (3%)				
T1am3/T1b sm	16 (53%)	49 (42%)	0.28	1.56 (0.70-3.50)		
T1bsm	6 (20%)	19 (16%)	0.64	1.28 (0.46-3.54)		
Histology subtype G2/G3	13 (62%)	45 (76%)	0.21	0.51 (0.17-1.47)		
Histology subtype G3	0	4 (3%)				
Endoscopy tumor size (mean±SD), cm	3.60±2.01	3.23±2.18	0.41	1.08 (0.90-1.29)		
Circumfere nce over 3/4	8 (27%)	30 (26%)	0.93	1.04 (0.42-2.59)		
Circumfere nce over 1/2	23 (77%)	78 (67%)	0.32	1.60 (0.63-4.06)		
R0 resection	26 (87%)	112 (97%)	0.05	0.23 (0.05-0.99)	0.31	0.36 (0.05-2.60)
CLR	22 (73%)	103 (89%)	0.04	0.35 (0.13-0.94)	0.56	0.66 (0.17-2.63)

OR: odds ratio; CI: confidence interval; IQR: interquartile range; HN cancer: head and neck cancer; HPC: hypopharyngeal cancer; LVI: lymphovascular invasion; CLR: complete local remission.

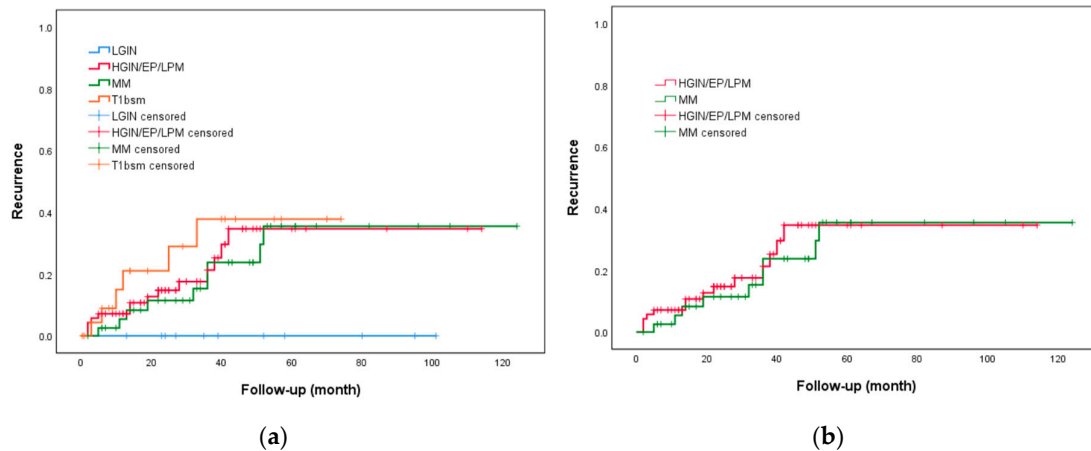


Figure 3. Kaplan-Meier curve for cumulative incidence of recurrence (a) No statistically significant difference was observed ($p=0.229$) from different pathologic stage.; (b) No statistically significant difference was observed ($p=0.63$) in HGIN/EP/LPM patients without additional therapy and MM patients without additional therapy.

4. Discussion

In this study, we investigated the long-term outcomes of patients with early ESCN after ESD with expanded indications, and observed favorable 5-year DSS (94.7%), en bloc resection (100%) and R0 resection (95.6%) rates following ESD for early ESCN in high-risk HNC patients. Regarding survival and disease recurrence, we found no significant difference between the patients with pT1a-MM and those with pT1a-EP/LPM. Our results suggest that ESD without additional therapy may be a reasonable treatment option for patients with ESCN involving pT1a-MM.

In contrast to the significant perioperative mortality rate associated with esophagectomy (previously reported as ranging from 1.5% to 12.5%), [6,21,22] ESD, as a minimally invasive procedure, has been associated with fewer perioperative comorbidities in selected patients with early ESCN [7–10]. Moreover, a previous study found that patients who underwent ESD had a lower risk of non-fatal severe adverse events compared to those who underwent esophagectomy for early ESCN (15.2% vs 27.7%; $P=0.001$) [6]. In the present study, ESD was not associated with any cases of perioperative mortality, and the post-ESD stricture rate was only 9.8%, which is consistent with the rates of 6% to 18.1% reported in large cohort studies with adequate stricture prevention [7,8,10,12,23]. Other advantages of ESD include the high en bloc and R0 resection rates, which have been reported to reach 95% to 100% and 84.5% to 99.3%, respectively, in Asian studies [23–26]. In comparison, reports from Western countries indicate varying R0 resection rates for ESD in early ESCN, ranging from 69.6% to 96.7% [11,27,28]. A previous prospective study reported a higher en bloc resection rate with ESD compared with endoscopic mucosal resection for early ESCN (100% vs 53.3%; $P=0.009$) [29]. In our study, we achieved favorable en bloc and R0 resection rates of 100% and 95.6%, respectively, consistent with previous research. In addition, the CLR rate in our study was 88%. Only a few studies have reported the CLR rate, including one study with a rate of 95.7% for ESD in cases with early ESCN [30], and another with a rate of 96.6% for Barrett's esophagus [31].

Regarding disease recurrence, a real-world cohort study comparing ESD with esophagectomy in selected patients with pT1a-LPM/MM and pT1b-SM (invading the submucosa layer) found no statistically significant difference in cancer recurrence or metastasis during the 21-month follow-up period (9.1% vs 8.9%; $P=0.948$) [6]. This suggests favorable long-term outcomes of ESD in selected early ESCN patients. In the present study, the only independent factor associated with disease recurrence was alcohol abstinence, aligning with findings from a previous prospective cohort study [32]. In multivariate analysis, neither R0 resection nor CLR was associated with a higher recurrence rate. This may be because all the patients who did not achieve R0 resection after ESD received additional therapy. Our 5-year local recurrence rate of 11% is in line with the range of 3.9% to 16.8%

reported in patients without HNC in large Japanese cohort studies [7–9]. Furthermore, the high metachronous recurrence rate of 17.9% after ESD in HNC patients reported in previous research was not observed in our study [12]. This finding may be associated with our high R0 resection rate and the significant prevalence of alcohol abstinence after education, notably among the patients with HNC.

Previous studies have reported cumulative 5-year metastatic recurrence rates for patients diagnosed with pT1a-EP/LPM and pT1a-MM ranging between 0%- 0.5% and 3.3%- 8.7% [7,9,10] respectively, which is consistent with our results. Due to an elevated rate of lymph node metastasis, the Japan Esophageal Society guidelines in 2017 recommended additional treatment after ESD for pT1a-MM ESCC patients [3]. However, an increasing number of studies suggests a positive prognosis in pT1a-MM patients after ESD even without additional therapy [10,33]. A recent study conducted in Japan found that ESD for pT1a-MM patients without LVI exhibited comparable DSS to pT1a-EP/LPM patients (99.3% vs 96.6%, $P=0.118$), with no significant differences in the cumulative incidence of metastatic and local recurrence ($P=0.121$ and $P=0.455$, respectively) [10]. Our data support these results, in that we observed no significant differences in OS, DSS or recurrence after ESD between the patients with pT1a-MM without additional therapy and those with pT1a-EP/LPM without additional therapy (**Figure 2a-2d** and **Figure 3b**). Even when considering the presence or absence of LVI, no statistically significant differences were observed between the two groups (**Figure 2b** and **2c**). Our findings suggest that expanding the indications for ESD without additional therapy to include pT1a-MM patients without LVI seems reasonable, and consistent with previous research [10]. Further research is required to confirm the clinical outcomes of pT1a-MM patients after ESD, and appropriate follow-up strategies need to be established.

The favorable outcomes of ESD for second primary early ESCN in the high-risk HNC patients in this study are also noteworthy. Even though the 5-year OS rate in our patients was only 48%, which is lower than the 95.1% to 99% reported in Japanese cohorts [8,9], the 5-year DSS reached 94.7%, which is not far from the 99.1% to 100% reported previously [8,9]. The lower OS in our cohort may be due to the significant proportion of patients with HNC (50%), among whom 53.4% were at stage IV (Table A1), with 50% of deaths related to HNC (Table A2). Similar findings were reported in a retrospective study involving 167 patients, 61.7% of whom were diagnosed with HNC [12]. The 10-year disease-related survival rate was more than 90%, whereas the OS rate was less than 70% [12]. We previously reported that screening and surveillance of ESCN by ME-NBI can provide opportunities for early treatment and even improve the survival of hypopharyngeal cancer patients [17]. Given the positive short-term and long-term outcomes observed in this study, we believe that ESD with expanded indications for second primary ESCN can provide clinical benefits with a favorable DSS rate. In addition, in our previous case-control study, tumors located in the hypopharynx and pharynx were associated with a higher risk of developing second primary ESCN in HNC patients (aOR 4.52, 95% CI: 1.46-13.99, $P=0.009$ and aOR 5.70, 95% CI: 1.08-29.99, $P=0.04$) [13]. However, the impact of HNC tumor site on recurrence after ESD for second primary early ESCN remains unclear. In the present study, although the presence of HNC was not significantly associated with recurrence (Table 3), there appeared to be a trend suggesting a higher incidence of recurrence in laryngeal and hypopharyngeal cancers compared to cancers of the oral cavity and oropharynx (Figure A2-A4). More studies are needed to determine the relationship between HNC tumor site and recurrence of second primary early ESCN after ESD.

Some limitations of this study should be noted. First, this study adopted a retrospective design, which may have introduced potential selection and measurement bias. Second, the limited number of pT1a-MM patients with concurrent LVI in this study undermines the reliability of assessing the statistical significance of LVI on clinical outcomes in the pT1a-MM subgroup. Third, the heterogeneity of the study population, including patients with HNC from various primary sites and those without HNC, may impact the generalizability of the findings.

5. Conclusions

In summary, our results showed favorable outcomes of ESD for second primary early ESCN in patients with HNC. We also found that ESD in patients with pT1a-MM yielded comparable results to those with pT1a-EP/LPM in terms of survival and disease recurrence. This highlights the potential for expanding the indications for ESD in managing pT1a-MM patients without additional therapy. Further research is necessary to validate these findings.

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Informed Consent Statement: The requirement for written informed consent was waived because of the absence of identifiable information in data analysis.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix

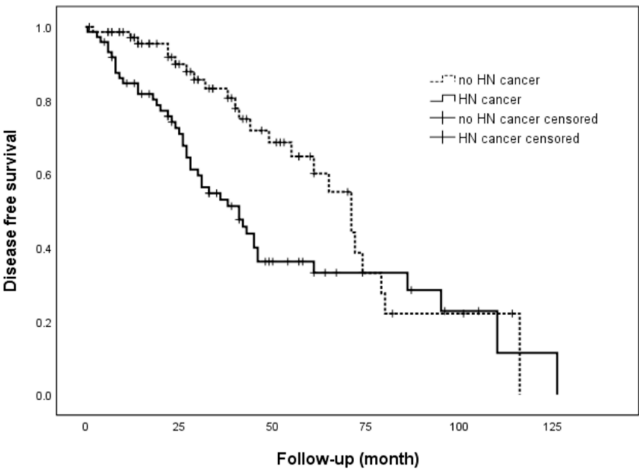


Figure A1. Kaplan-Meier curve of the impact of head and neck cancer on disease free survival. Significantly higher survival was observed in patients without head and neck cancer (p=0.013).

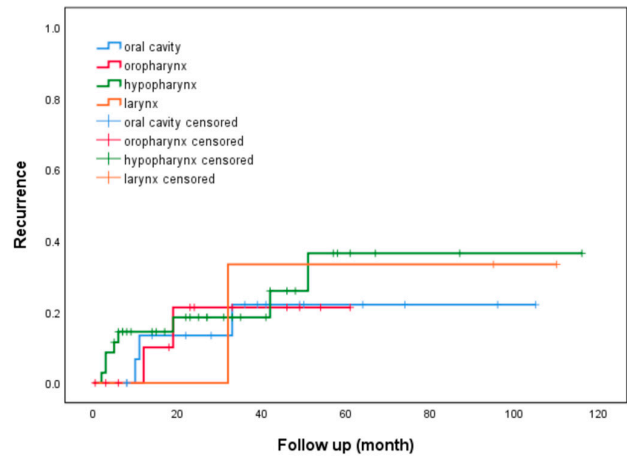


Figure A2. Kaplan-Meier curve of the impact of head and neck cancer location on recurrence. No statistically significant was observed (p=0.915).

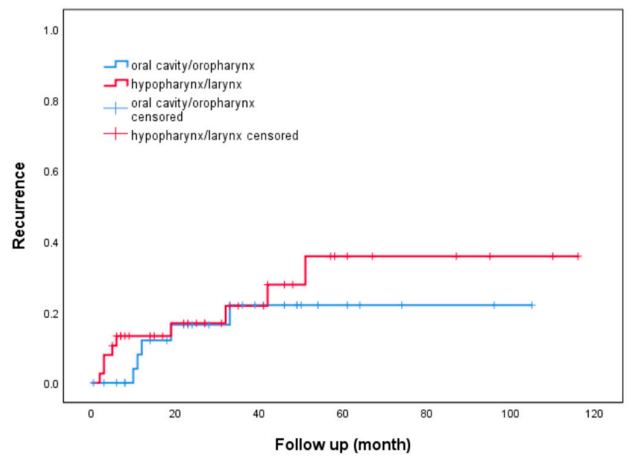


Figure A3. Kaplan-Meier curve of recurrence in patients with oral cavity/oropharyngeal cancer and hypopharyngeal/laryngeal cancer. No statistically significant was observed (p=0.476).

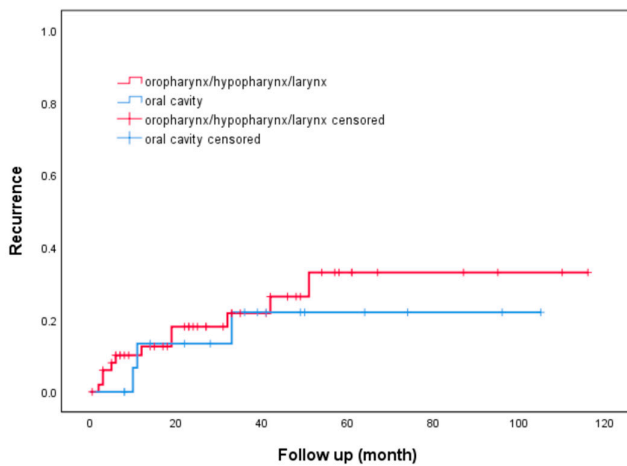


Figure A4. Kaplan-Meier curve of recurrence in patients with oral cavity cancer and oropharyngeal/hypopharyngeal/laryngeal cancer. No statistically significant was observed (p=0.61).

Table A1. Location and staging of 73 head and neck cancer patients.

		Number of patients (%)
Location of head and neck cancer		
Oral cavity		18 (24.7)
	Oropharynx	13 (17.8)
	Hypopharynx	36 (49.3)
	Larynx	3 (4.1)
	Other location ¹	3 (4.1)
Stage of head and neck cancer		
	I	5 (6.8)
	II	8 (11.0)
	III	21 (28.8)
	IV	39 (53.4)

¹ Other location of head and neck cancer includes tracheal cancer and thyroid cancer.

Table A2. Causes of death.

	Number of patients (%)
Head and neck cancer	24 (50)
Pulmonary comorbidities ¹	8 (16.7)
Other cancer ²	4 (8.3)
Esophageal cancer	3 (6.3)
Liver cirrhosis	2 (4.2)
Complication of esophagectomy	1 (2.1)
Other ³	6 (12.5)

¹ Pulmonary comorbidities includes pneumonia with respiratory failure, chronic obstruction pulmonary disease and idiopathic pulmonary fibrosis. ² Other cancer includes lymphoma, colon cancer and lung cancer. ³ Other causes of death includes myocardial infarction, cerebral vascular accident and complication of tracheostomy.

Table A3. Outcomes of patients with and without HN cancer after ESD.

Variable, Patients No. (%)	All patients (n=146)	HN cancer (n=73)	Without HN cancer (n=73)	P Value (HN cancer vs without HN cancer)
Overall survival				
1-year	124 (91.9)	60 (85.7)	64 (98.5)	0.007
3-year	66 (67.3)	30 (53.6)	36 (85.7)	0.001
5-year	36 (48)	17 (37)	19 (65.5)	0.018
Disease-specific survival				
1-year	134 (99.3)	69 (98.6)	65 (100)	0.33
3-year	96 (98)	55 (98.2)	41 (97.6)	0.84
5-year	71 (94.7)	45 (97.8)	26 (89.7)	0.13
Disease-free survival				
1-year	112 (83.6)	52 (75.4)	60 (92.3)	0.008
3-year	49 (51.6)	26 (46.4)	23 (59)	0.23

5-year	24 (32.9)	14 (31.8)	10 (34.5)	0.81
Local recurrence	30 (20.5)	16 (21.9)	14 (19.2)	0.68

HN cancer: head and neck cancer; ESD: endoscopic submucosal dissection.

Table A4. Additional therapy utilization in 19 Patients, 8 due to R1 resection.

		Number of patients (%)
Type of additional therapy		
CCRT		13 (68.4)
	Esophagectomy	5 (26.3)
	RT alone	1 (5.3)
Stage		
	HGIN	1 (5.2)
	T1am3	4 (21.1)
	T1bsm1	3 (15.8)
	T1bsm2	11 (57.9)
Reasons of additional therapy		
	R1 resection	8 (42.1)
	pT1bsm2	5 (26.3)
	pT1bsm1, LVI(+)	2 (10.5)
	pT1am3, LVI(+)	2 (10.5)
	pT1am3, LVI(-)	1 (5.3)
	Other ¹	1 (5.3)

CCRT: concurrent chemoradiotherapy; ESD: endoscopic submucosal dissection; RFA: radiofrequency tumor ablation; RT: radiotherapy; LVI: lymphovascular invasion. ¹ One patient underwent esophagectomy due to initial pathological misdiagnosis.

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