International Journal of Gerontology 14 (2020) 288–292
https://doi.org/10.6890/IJGE.202011_14(4).0007

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

The Effectiveness and Safety of Endoscopic Submucosal Dissection for Early Esophageal Squamous Neoplasm in the Elderly

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ARTICLE INFO

Accepted 11 March 2020

Keywords:
endoscopic submucosal dissection,
esophageal neoplasm,
elderly

SUMMARY

Background: Endoscopic submucosal dissection (ESD) can be used as a minimally invasive treatment in the early stages of esophageal squamous cell carcinoma (ESCC). Due to the higher frequency of underlying illnesses, the superiority of ESD to esophagectomy is more prominent in the elderly than in the non-elderly. This study compared the efficacy and safety of ESD for early ESCC between the elderly and non-elderly patients.
Methods: From August 2014 to December 2019, 59 patients treated with ESD for early ESCC were retrospectively analyzed. The elderly group (n = 20) comprised patients aged ≥ 65 years, and the non-elderly group (n = 39) comprised those aged < 65 years. Clinical and pathological results, including R0 resection, curative resection, survival, and complication rates were compared between the groups.
Result: Both groups were male predominant (elderly: 80%, non-elderly: 87.2%), and the tumor was mostly found in the mid thoracic (elderly: 40%, non-elderly: 61.5%). Tumor size, depth of tumor, and lymphovascular invasion were not significantly different between the groups. Tumor occupying ≥ 3/4 circumference of the esophagus was only found in the non-elderly group (elderly: 0, non-elderly: 8; p = 0.036). The R0 resection rate (elderly: 100%, non-elderly: 94.9%, p = 0.544), curative resection rate (elderly: 80%, non-elderly: 79.5%, p = 1), recurrence rate (elderly: 10%, non-elderly: 10.3%, p = 1), follow-up period (elderly: 20.4 ± 16.8 months, non-elderly: 21 ± 17.6 months, p = 0.904), and post ESD stricture (elderly: 5%, non-elderly: 7.7%, p = 1) were similar between the two groups. The elderly had longer hospital stays than the non-elderly, but without a significant difference (elderly: 5 ± 1.4 days, non-elderly: 4.3 ± 1.3 days; p = 0.08). Post ESD stricture was correlated with the tumor circumference (p = 0.001). Cox model stratified by age groups, adjusting for other factors, non-curative ESD and concurrent other malignancy were associated with increased 5.5-year mortality (hazard ratio 6.30; 95% CI, 1.03–38.68; hazard ratio 13.78; 95% CI, 1.50–126.48).
Conclusion: ESD was effective and safe for early ESCC in the elderly.

1. Introduction

Esophageal cancer is the third most common cancer in the Chinese population.[1] In Asia, more than 90% of primary esophageal malignancies are squamous cell carcinomas.[2,3]

In the past, the standard treatment for esophageal squamous cell carcinoma (ESCC) was radical esophagectomy or chemoradiotherapy. However, the elderly have more comorbidities and poorer cardiopulmonary functions than younger patients, thereby resulting in more adverse effects and higher mortality rates after these standard treatments.[4]

With the advancement of endoscopic diagnostic technology, the detection of early esophageal cancers has become improved. Endoscopic submucosal dissection (ESD), a procedure that has become more established and popular in recent years, can be used as a minimally invasive treatment for patients with superficial ESCC. Moreover, ESD also achieves en bloc resection, which offers low rates of complication and risks of lymph node metastasis as supported by histopathological evidence.[5] According to the Japanese Esophageal Society (JES) guidelines, tumor limiting within the mucosal layer (T1a) is rarely associated with lymph node metastasis and is an absolute indication for endoscopic resection, whereas tumor invading the mucosa muscularis or less than 200 μm into the submucosal layer (T1b-SM1) may have a small risk of lymph node metastasis and is defined as a relative indication for endoscopic resection. Additional esophagectomy or chemoradiotherapy is recommended if lymph node involvement is suspected after clinical and histopatholgical evaluations.[6]

While the safety and efficacy of ESD for early gastric neoplasm in elderly patients have been reported,[7,8] limited studies have reported on the safety and efficacy of ESD for superficial ESCC in elderly patients. Therefore, this study aimed to investigate whether ESD treatment has different outcomes between younger and elderly (≥ 65 years) patients.

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2. Materials and methods

The study was approved by the institutional review committees at MMH in Taiwan (IRB No. 20MMHIS076e), and all included patients and their surrogates provided written informed consent.

2.1. Study design

From August 2014 to December 2019, 59 patients with superficial esophageal neoplasm who underwent ESD in a tertiary care hospital were consecutively enrolled in this retrospective study. Among these patients, 20 who were aged ≥ 65 years were assigned to the elderly group, whereas 39 who were aged < 65 years were assigned to the non-elderly group. Patients who met the following criteria were included in this study: (1) endoscopic signs of early lesions confirmed on narrow band image with magnification, i.e., intrapapillary capillary loop (IPCL) type V-1~type V-3 (V-1: dilatation, meandering, irregular caliber, and form formation of IPCL, and which means carcinoma in situ; V-2: extension of IPCL type V1, which implies tumor invasion deeper but within mucosal layer; V-3: advanced destruction of IPCL, which means tumor invading over mucosa muscularis but less than 200 μm into the submucosal layer) or JES type B1~B2 vessels (abnormal microvessels with severe irregularity or highly dilated abnormal vessels. Type B1: vessels with a loop like formation, and means tumor within mucosal layer. Type B2: vessels without a loop like formation, and means tumor invading into mucosa muscularis or less than 200 μm into the submucosal layer);[9,10] (2) no signs of lymph node or distant metastasis reflected on computed tomography (CT) scan or positron emission tomography (PET); and (3) postoperative pathological diagnosis of high-grade intraepithelial neoplasia (HGIN), or ESCC within the submucosal layer.

Clinical information and endoscopic records were collected and analyzed.

2.2. Endoscopic procedure and postoperative management

All patients were placed under general anesthesia for the standard ESD method (Figure 1).[11] Patients were only administered fluid supplements and nothing by mouth for 24 hours after tumor resection. In addition, parenteral proton pump inhibitors and antibiotics were administered for 3 days. For the prevention of post-ESD esophageal stricture, systemic steroids which provides anti-inflammation activity and reduce the collagen content were administered in patients with mucosal defect in > 75% of the circumferential esophageal lumen.[12,13]

2.3. Data collection and follow up

Clinicopathological information and endoscopic records were collected and analyzed. All patients were scheduled for surveillance esophagogastroduodenoscopy (EGD) within 3–6 months to monitor wound healing and detect for local tumor recurrence. Chest CT or PET was scheduled every 6–12 months to detect the occurrence of distant metastasis.

Tumor location was divided into the upper thoracic (from incisor teeth (IT) 15–23 cm), mid-thoracic (IT 24–32 cm), and lower thoracic (IT 33–45 cm) esophagus. R0 resection was defined as en bloc resection with margins free of tumor. Curative resection was defined as R0 resection without lymphovascular invasion, poor differentiation, or submucosal invasion of > 200 μm. Procedure time indicates the interval from marking the lesion to complete submucosal dissection. Perforation signifies free air detected by CXR or CT after ESD. Post-ESD bleeding was recorded as melena or hematochezia, which required emergency EGD or blood component therapy. Post-ESD stricture is defined as the presence of dysphagia requiring endoscopic treatment. Recurrence denotes local recurrence detected by EGD or distal metastasis detected by CT or PET.

2.4. Statistical analysis

Statistical analysis was performed with SAS version 9. (SAS Institute Inc., Cary, NC USA). Quantitative data were expressed as mean ± SD. Categorical variables were compared with the Chi-squared test or Fisher's exact test, and continuous variables were compared with the Student's *t* test. The level of significance was set at 0.05 and at a 2-sided level. Statistical methods with the Chi-

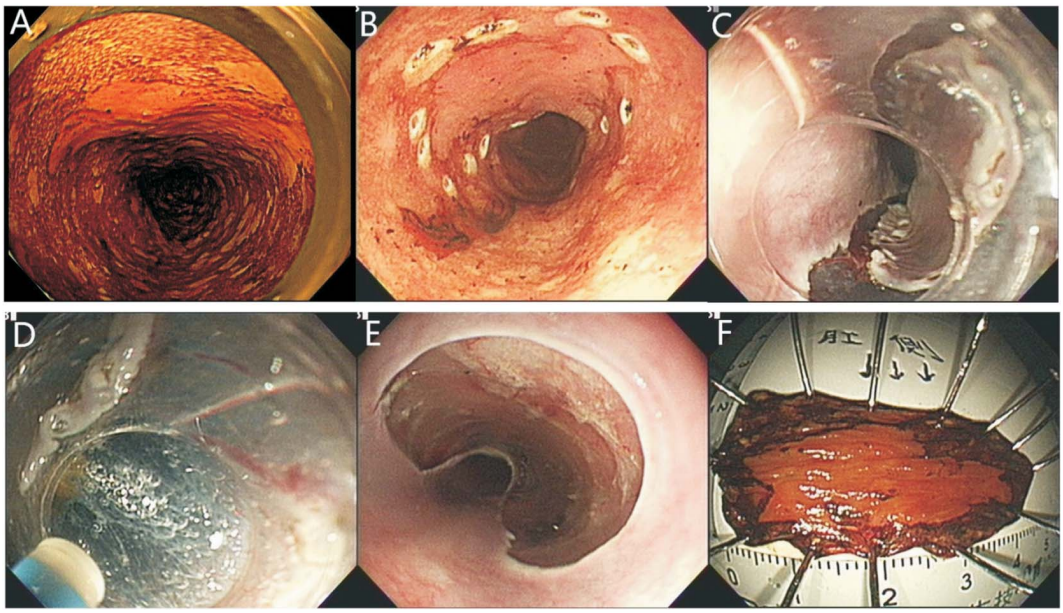

Figure 1. Endoscopic submucosal dissection procedure. (A) Superficial ESCC was identified by Lugol's solution. (B) Mark around the lesion. (C) Circumferential mucosal incision after submucosal injection with mixture of normal saline, diluted epinephrine and indigo carmine. (D) Submucosal dissection by Dual knife. (E) Check bleeding after complete submucosal dissection. (F) Fixed the tissue and stain the specimen with Logol's solution.

squared test, Fisher's exact test or the Student's *t* test were used for measurements of outcomes with ESD resections, tumor recurrence, and follow-up time.

Survival was measured from cancer diagnosis to death or last follow-up through December 2019. Kaplan-Meier curves were made to compare survival between elderly and non-elderly groups, and the log-rank test was used to compare the survival distributions of two groups. Cox proportional hazards models were used to evaluate age groups (elderly versus non-elderly) and other covariates and their association with survival time. We included the clinically meaningful covariates including curative ESD and concurrent other malignancy in multivariable models. For 5.5-year survival analysis, patient survival times were censored at 5.5 years. Multivariate cox models stratified by age groups limiting the cohort to patients diagnosed from 2014 to 2018 were developed.

3. Result

3.1. Baseline characteristics of patients

Clinical features of the recruited patients are summarized in Table 1. The mean ages of patients were70.0 ± 6.3 years and 53.4 ± 5.9 years in the elderly (n = 20) and non-elderly (n = 39) groups respectively (p < 0.001). Males were predominant in both groups (elderly group: 80%; non-elderly group: 87.2%). The tumors were located in the mid-thoracic segment (elderly group: 40%; non-elderly group: 61.5%), followed by the lower (elderly group: 35%; non-elderly group: 28.2%) and upper (elderly group: 25%; non-elderly group: 10.3%) thoracic segments. Only 8 patients in the non-elderly group had tumors ≥ 3/4 circumference of the esophagus (elderly group: 0%, non-elderly group: 20.5%; p = 0.036). As with other malignancies, the tumor size, depth of tumor invasion, lymphovascular invasion, and number of poorly differentiated tumors were not significantly different between the two groups.

3.2. Short-term outcomes and complications of ESD

Short-term outcomes and complications of ESD are shown in Table 2 and Table 3. The procedure time was 80.3 ± 63.7 minutes in the elderly group and 92.8 ± 109.4 minutes in the non-elderly group (p = 0.639). Patients in the elderly group had a longer hospital stay than those in the non-elderly group (5 ± 1.4 days vs. 4.3 ± 1.3, p = 0.08).

The R0 resection (elderly group: 100%, non-elderly group: 94.9%; p = 0.544) and curative resection (elderly group: 80%, non-elderly group: 79.5%; p = 1.000) rates were similar in both groups. All

Table 1
Baseline characteristics in elderly and non-elderly group.

	Elderly (n = 20)	Non-elderly (n = 39)	Total (n = 59)	p
Age (years), mean ± SD	70.0 ± 6.3	53.4 ± 5.9	59 ± 9.9	< 0.001 [a]
Male, no. (%)	16 (80.0)	34 (87.2)	50 (84.7)	0.471 [b]
Tumor location, no. (%)				0.200 [c]
Upper thoracic	5 (25.0)	4 (10.3)	9 (15.3)	
Middle thoracic	8 (40.0)	24 (61.5)	32 (54.2)	
Lower thoracic	7 (35.0)	11 (28.2)	18 (30.5)	
Tumor size (cm), mean ± SD	41.7 ± 12.9	41.9 ± 27.8	41.9 ± 23.9	0.978 [a]
Circumference of the tumor, no. (%)				0.036 [c]
< 1/4	4 (20.0)	8 (20.5)	12 (20.3)	
≥ 1/4, < 2/4	11 (55.0)	21 (53.9)	32 (54.2)	
≥ 2/4, < 3/4	5 (25.0)	2 (5.1)	7 (11.9)	
≥ 3/4	0 (0.0)	8 (20.5)	8 (13.6)	
Depth of invasion, no. (%)				0.423 [c]
M1	9 (45.0)	16 (41.0)	25 (42.4)	
M2	1 (5.0)	1 (2.6)	2 (3.4)	
M3	8 (40.0)	15 (38.5)	23 (39.0)	
SM1	1 (5.0)	0 (0.0)	1 (1.7)	
SM2, SM3	1 (5.0)	7 (17.9)	8 (13.6)	
Lymphovascular invasion, no. (%)				0.598 [b]
Positive	2 (10.0)	2 (5.13)	4 (6.8)	
Poorly differentiated, no. (%)	1 (5.0)	2 (5.13)	3 (5.1)	1.000 [b]
Other malignancy, no. (%)*	4 (20.0)	12 (30.8)	16 (27.1)	0.0183 [b]

Categorical variables were reported as percentages and continuous variables as mean (SD).
a: *t* test. b: Fisher's exact test. c: Chi-squared test.
*: Elderly group: 3 hypopharyngeal cancer, 1 lung cancer. Non-elderly group: 6 hypopharyngeal cancer, 4 oral cancer, 2 tonsil cancer.

Table 2
Outcomes and complications in elderly and non-elderly group.

	Elderly (n = 20)	Non-elderly (n = 39)	Total (n = 59)	p
Procedure time (min.), mean ± SD	80.3 ± 63.7	92.8 ± 109.4	88.6 ± 95.9	0.639 [a]
Hospital stay (day), mean ± SD	5 ± 1.4	4.3 ± 1.3	4.5 ± 1.3	0.08 [a]
R0 resection, no. (%)	20 (100.0)	37 (94.9)	57 (96.6)	0.544 [b]
Curative resection, no. (%)	16 (80.0)	31 (79.5)	47 (79.7)	1.000 [b]
Recurrence, no. (%)	2 (10.0)	4 (10.3)	6 (10.2)	1.000 [b]
Survival (months), mean ± SD	20.4 ± 16.8	21 ± 17.6	20.8 ± 17.2	0.904 [a]
Stricture, no. (%)	1 (5.0)	3 (7.7)	4 (6.8)	1.000 [b]

Categorical variables were reported as percentages and continuous variables as mean (SD).
a: *t* test. b: Fisher's exact test.

Table 3
Correlation between circumference of the tumor and post ESD stricture.

Circumference of the tumor	Stricture, no. (%)		p
	Yes	No	
< 1/4	0 (0.0)	12 (100.0)	0.001
≥ 1/4, < 2/4	0 (0.0)	32 (100.0)	0.001
≥ 2/4, < 3/4	1 (14.3)	6 (85.7)	0.001
≥ 3/4	3 (37.5)	5 (62.5)	0.001

Categorical variables were reported as percentages.
a: Chi-squared test.

patients were followed until death or until December 2019. Kaplan-Meier curves showing overall survival by treatment approach up to 5 years after diagnosis are shown in Figure 2, and there is no difference in unadjusted 5-year survival by treatment approach (p = 0.550 by log-rank test).

Two patients (10%) in the elderly group had recurrence, with a mean recurrence time of 32 months post-ESD. Both of them had curative tumor resection. One patient had stage IV hypopharyngeal cancer, and the other patient's pathology was poorly differentiated. Four patients (10.3%) in the non-elderly group had recurrence, with a mean recurrence time of 15 months post-ESD. One patient did not achieve curative resection (tumor invasion > 200 μm in the submucosal layer), and another patient had oral cancer concurrently.

Total four patients (two elderly patients, and two non-elderly patients) had lymphovascular invasion in histopatholgical evaluation. One elderly patient and one non-elderly patient underwent further esophagectomy. One elderly patient did not receive any other treatment because of severe chronic obstructive lung disease (COPD). One non-elderly patient concurrently had terminal stage of tonsil cancer, and refused further esophagectomy.

The one-year mortality rate in elderly group and non-elderly group was 5% (1/20) and 2.6% (1/39), respectively (OR: 0.5 [95% confidence interval, 0.030–8.439]). There is higher five-year mortality rate in non-elderly group (4/39, 10.3%) than in elderly group (1/20, 5%) (OR: 0.22 [95% confidence interval, 0.23–20.83]). One patient in the elderly group died 6 months post-ESD due to severe COPD. Four non-elderly patients died for terminal stages of other malignancies: two had tonsil cancer, one had oral cancer, and one had hypopharyngeal cancer. Cox model stratified by age groups, adjusting for other factors, non-curative ESD and concurrent other malignancy were associated with increased 5.5-year mortality (hazard ratio 6.30; 95% CI, 1.03–38.68; hazard ratio 13.78; 95% CI, 1.50–126.48) (Table 4).

Esophageal stricture post-ESD (37.5%) was evident in patients with tumors ≥ 3/4 circumference of the esophageal lumen (p = 0.001).

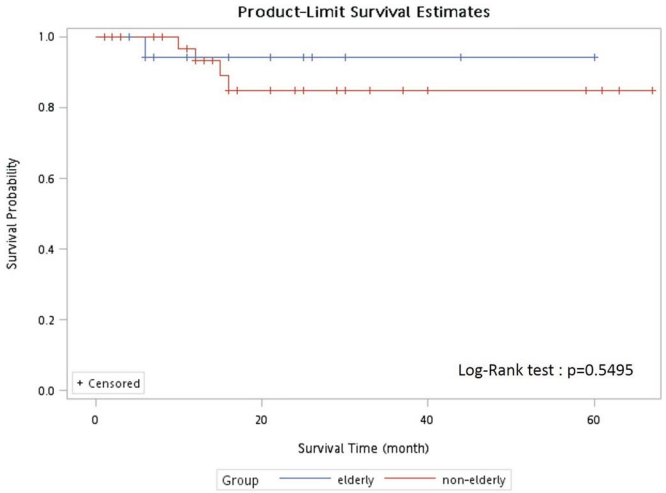

Figure 2. Kaplan-Meier overall survival curve for elderly and non-elderly patients undergoing esophageal endoscopic submucosal dissection.

4. Discussion

The elderly population has more coexisting cardiovascular and respiratory diseases before surgery than younger adults.[14] In a large retrospective study for esophagectomy in the elderly, patients aged ≥ 70 years had higher nonsurgical complications (35% vs. 27%, p < 0.05), higher operative mortality (8.4% vs. 3.8%, p < 0.05), higher hospital mortality (11.6% vs. 5.4%, p < 0.05), and lower 5-year survival (27% vs. 34%, p < 0.05) than those aged < 70 years.[15] Endoscopic treatments such as ablation, local tumor destruction, and endoscopic mucosal resection (EMR) have been proven to result in shorter hospital stays, lower adverse effects, and better 2-year survival than esophagectomy in the elderly population.[16] While the superiority of ESD for superficial esophageal neoplasms has been proven,[17] there are limited reports on esophageal ESD in the elderly.[18,19]

In our study, the elderly and non-elderly groups had high R0 resection rates, and the curative resection rate was approximately 80%, similar to that reported in a previous study.[19] There was no difference in the recurrence and short-term survival rates between the groups. The duration of hospital stay was longer in the elderly group, which could be due to a higher prevalence of underlying illnesses in this group, thereby resulting in longer recovery. No perforation or delayed bleeding was found post-ESD in our study. Four patients had esophageal strictures, which correlated with the circumference of tumor (p = 0.001) but not with age. This finding was consistent with that reported in previous studies.[17,20]

According to the JES guidelines, the absolute indication for esophageal ESD is neoplasm limiting within the mucosal layer (T1a). Relative indication denotes tumors invading the mucosa muscularis or < 200 μm into the submucosal layer (T1b-SM1). This may have a small risk of lymph node metastasis, and additional treatment should be considered if lymhovascular invasion is found in pathology. Additional esophagectomy should be performed in ESCC patients with deep submucosal invasion, i.e., tumor invasion > 200 μm in the submucosal layer (SM2). However, many elderly patients have comorbidities and cannot tolerate esophagectomy. A recent study revealed that the 5-year survival rate in an SM1 ESCC elderly patient who underwent ESD without additional treatment was comparable to that in a T1a ESCC elderly patient post-ESD.[21] Moreover, one

Table 4
Multivariate cox proportional hazard regression analysis stratified by age groups, adjusting for other factors.

Parameter	Estimate	Standard error	p	HR	95% confidence interval of HR
Elderly vs. non-elderly	-0.553	1.129	0.624	0.575	0.063–5.250
Concurrent other malignancy vs. non-concurrent other malignancy	2.977	1.270	0.020*	13.784	1.502–126.484
Non-curative ESD vs. curative ESD	1.125	1.174	0.047*	6.297	1.025–38.677

HR, hazrd ratio.
* Significant values (p < 0.05) are presented.

recent prospective Japanese multicenter study showed that the efficacy of endoscopic resection combined with selective chemoradiotherapy was comparable to that of surgery in T1b (SM1-2) ESCC patients.[22] Another study also found no significant relationship between lymph node metastasis in T1 ESCC and long-term survival rate.[23] Together with previous literature, our study has pointed out that esophageal ESD can be performed in elderly patients with the same safety and efficacy as in younger patients. Although there were doubts on T1b SCC-associated lymph node metastasis, ESD should still be considered as a first-line treatment in the elderly patients with early ESCC, taking into account the comorbidities of elderly patients, chances of adverse effects, and short-term survival.

This study demonstrated the correlation between tumor circumference and post-ESD stricture. Some studies have also proved post-ESD stricture was not correlated with age of patient.[18,19] Although no esophageal strictures were found in the elderly patients in this study, this is an important matter as post-ESD esophageal stricture would significantly affect patients' quality of life and require repeated endoscopic treatments.[24] Long-term endoscopic interventions for esophageal strictures increase the risk of fatal complications such as esophageal perforation and mediastinitis in elderly patients.

There are some limitations in the present study. Our sample size was small, and this was a retrospective, single-center study. In addition, the follow-up time taken to evaluate the outcome could be insufficient. Therefore, further investigation should be performed to validate that the efficacy and safety of ESD procedure are indeed similar in the elderly and non-elderly patients with superficial ESCC.

Declaration of interests

We declare no competing interests. The authors have no conflicts of interest relevant to this article.

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