의학석사 학위논문

식도 종양에 대해 내시경적 점막하 절제술을 시행한 환자에서 천공의 유병률과 위험인자

Prevalence and risk factors of perforation after endoscopic submucosal dissection for esophageal neoplasm

울산대학교 대학원

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정 준 용

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이 논문을 의학석사 학위 논문으로 제출함

2020년 2 월

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Abstract

AIM: To investigate prevalence and risk factors of esophageal perforation and which anesthesia is appropriate associated with esophageal endoscopic submucosal dissection (ESD) for esophageal neoplasm.

Methods: We retrospectively analyzed 507 esophageal ESD lesions from October 2007 to February 2019 in Asan Medical Center. Binary regression logistic analysis and multivariate analysis were used to investigate the risk factors of perforation after esophageal ESD. Additionally, we compared general anesthesia (GA) and under conscious sedation (UCS) to find out perforation occurrence by anesthesia method since November 2010 when GA mainly conducted. 1:6 matching was performed based on observed covariate (tumor long axis, invasion depth, circumference) thought to be affect perforation. Outcome analysis was performed using GEE (Generalized estimating equation) or Linear mixed model that accounts for the clustering of matched pairs.

Results: Esophageal perforation occurred in 24 of 507 cases (4.7 %) after esophageal ESD. UCS (OR= 3.861, 95% CI, 1.429– 10.42, P=0.008) and larger circumference (OR=3.465, 95% CI, 2.046– 5.955, P<0.001) were associated with esophageal perforation after ESD in total period investigation. Age (OR=1.007, 95% CI, 0.690– 1.056, P=0.773), sex (OR=1.687, 95% CI, 0.221– 12.88, P=0.614), underlying disease (OR=0.599, 95% CI, 0.264– 1.362, P=0.222), invasion depth (OR=1.333, 95% CI, 0.441– 4.023, P=0.61), histology (OR=6.624, 95% CI, 0.884– 49.61, P=0.066), predominance (OR=1.541, 95% CI, 0.661– 3.588, P=0.316), longitudinal location (OR=1.033, 95% CI, 0.946– 1.129, P=0.469), and direction (OR=0.434, 95% CI, 0.168– 1.120, P=0.085) were not significant.

However, there was no significant statistical difference in perforation (OR=5.952, 95% CI, 0.365− 100.0, P=0.2106) and other complications (OR=0.856, 95% CI, 0.097− 7.566, P=0.889) when compared with GA and UCS after GA was mainly used.

Conclusions: Larger circumference and UCS were considered as risk factors of perforation after esophageal ESD, but there was no significant difference of perforation by anesthesia method (OR=5.952, 95% CI, 0.365− 100.0, P=0.2106) when circumference was less than 25 %. Therefore, it is reasonable to choose methods of anesthesia by circumference of esophageal neoplasm.

Keywords: Esophageal neoplasm; Endoscopic submucosal dissection; Risk factors; Perforation; Anesthesia

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Introduction

Esophageal cancer has a poor prognosis, with a 5-year survival rate of only 15 to 25 %, with cancer-related deaths ranking sixth and is the eighth most common cancer in the world.(1-4) Because esophageal cancer has a high mortality rate and is often diagnosed after progression, it is important to early detect and treat esophageal neoplasm, including esophageal dysplasia and endoscopy is a standard method for diagnosis and treatment.(3, 4) Unlike advanced esophageal cancer, superficial esophageal cancer (SEC) can be treated with esophageal resection. In Asia, in particular, endoscopic therapy is more aggressively performed than in the West, and there is nearly no difference in survival rate between surgical and endoscopic treatment in SEC.(4, 5) Endoscopic submucosal resection (ESD) is currently available as a standard treatment in endoscopic resection of esophageal dysplasia and SEC, and can completely remove regardless of size and has a good therapeutic effect.(6) Thus, ESD for esophageal neoplasm is gradually increasing.

Esophageal perforation is the second most complication associated with esophageal ESD,(7, 8) but there is little research on risk factors of perforation and clinical course or prognosis when it happens. Furthermore, esophageal perforation can cause mediastinal emphysema or mediastinitis. Because it can be life-threatening, it is important to be aware of risk factors of perforation and so that perforation does not occur.(9) Recently, most esophageal ESD is usually performed under general anesthesia (GA), but GA in all patients seems inefficient and there’ re no exact guidelines about it.(10) Based on our clinical data, we would like to investigate the prevalence and risk factors of esophageal perforation including types of anesthesia.

Methods

Study population

We conducted a retrospective study on patients who underwent ESD for esophageal neoplasm at Asan Medical Center, Seoul, South Korea. In this study, we included 507 ESD lesions and 454 patients who underwent ESD aged 31–86 years from October 2007 to February 2019. Esophageal neoplasm includes esophageal dysplasia and superficial esophageal squamous cell carcinoma and adenocarcinoma based on final pathologic reports.

We described esophageal lesion's locations, predominance, circumference, direction, size, and macroscopic types according to Paris endoscopic classification based on the endoscopic image. (11) All patients confirmed esophageal cancer on final pathologic reports underwent computed tomography (CT) scans of the chest and abdomen, esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS) and positron emission tomography (PET) to investigate distant metastasis and tumor invasion depth. If esophageal neoplasm is confined to the mucosal layer and there are no distant metastasis or lymph node metastasis, we performed curative esophageal ESD.

All data was obtained from electrical medical records (EMR), including radiologic images like chest X-ray, chest CT, endoscopic images, final pathologic reports, endoscopy record sheets, laboratory tests, length of hospitalization stay and patients-related information like sex, age, previous ESD history, and underlying disease. The institutional review board at Asan Medical Center, Seoul, Korea, approved the study. (2019-0567) The study was performed according to the ethical principles of the Declaration of Helsinki.

Esophageal ESD protocols

Six endoscopy specialists (J.H.Y., C.K.D., S.H.J, D.H.K., J.H.L., J.Y.A.) performed EGD and esophageal ESD under GA or under conscious sedation (UCS) after positioning patients at left decubitus. Before November 2010, most procedures performed under UCS, but after that, most ones underwent GA. The typical ESD procedures at our institution included marking, mucosal incision, and submucosal dissection with simultaneous hemostasis, and have been previously described. Transparent cap (D-201-11814, Olympus) was attached to the tip of the forward-viewing endoscope (GIF-H260, Olympus) during the procedure. Before the esophageal ESD, white-light endoscopy (WLE), narrow band imaging (NBI), Lugol chromoendoscopy (LCE) were performed to confirm the location, circumference, and boundary of the lesions. We marked lesion's border and injected normal saline containing a small amount of 0.005 % epinephrine and indigo carmine after LCE. Esophageal ESD was performed after mucosal cutting the edge of the lesion using insulated-tip (IT) knife (Olympus), nano-IT knife (Olympus), Dualknife (Olympus), and/or hook knife (Olympus). Hemostasis was performed using hemostatic forceps (FD-410LR, Olympus) according to bleeding severity. We routinely check chest X-ray after procedure. If the patient’s condition was stable after treatment without complications, the patient was fasted for a certain time and proceeding from water to liquid fluid and discharged from the hospital after that.

After the procedure, EGD was performed every 6 months for up to 2 years, and every year thereafter. A biopsy was performed when suspected recurrence was identified. When esophageal cancer was confirmed on final pathologic reports, chest, abdominal CT scans, PET scans were performed. If the lesion is appropriate for ESD according to the protocol, the procedure was performed in the same way.

Perforation

Perforation was classified by macroperforation and microperforation. Macroperfortion was defined that endoscopically confirmed that the proper muscle layer was torn during the procedure. Although macroperforation was not identified during the procedure, microperforation was defined as the case when subcutaneous emphysema, pneumothorax, and pneumomediastinum were found in the post-procedure chest X-ray or chest CT scans.

In case of macroperforation, endoscopic clipping was attempted during the procedure, promptly. If endoscopic closure was performed successfully, fasting and intravenous antibiotics were administered for a certain time after the procedure. Thereafter, conservative care was conducted depending on the patient's clinical course. In case of microperforation was confirmed on the radiologic images after the procedure, fasting and intravenous antibiotics were administered for a certain time after the procedure. Thereafter, conservative care was conducted depending on the patient's clinical course in the same way as macroperforation. After conservative treatment for several days, if the patient's clinical course was stable and radiologic images such as pneumomediastinum did not progress, discharge from the hospital was confirmed.

Statistical analysis

Based on the information obtained from EMR, patients were divided into perforated and non-perforated groups. Baseline characteristics were compared using Chi-square test or Fisher's exact for categorical variables and T-test for continuous variables. Some continuous variables were transformed using log to normalize their distribution. To investigate the risk factors of perforation, the binary logistic regression analysis was used to

determine the odds ratios of the factors clinically thought to be affect perforation. Multivariate analysis was used to determine the risk factors for perforation of factors with P−value of less than 0.2 in univariate analysis, except for those that were highly correlated clinically and statistically using the correlation coefficient. To compare the efficacy and safety of anesthesia, UCS and GA groups were matched and compared since November 2010 when GA began in earnest. 1:6 matching was performed based on observed covariate (tumor long axis, invasion depth, circumference). Outcome analysis was performed using GEE (Generalized estimating equation) or Linear mixed model that accounts for the clustering of matched pairs. All statistical analyses were performed using SPSS version 21.0 (SPSS Inc. Chicago, IL., USA).

Results

Baseline characteristics

The baseline characteristics of the study samples were summarized in Table 1. We conducted a retrospective study based on clinical data of 507 esophageal ESD lesions of 454 patients. Mean age was 65.2 ± 8.7. Male sex was 473 (93.3 %). Mean hospital stay was 5.2 ± 3.0 days. Esophageal perforation occurred total 24 (4.7 %) and macroperforation and microperforation were 8 (1.6 %) and 16 (3.2 %), respectively. Previously history of ESD was 50 (9.9 %). Total patients with underlying diseases were 314 (61.9 %). Histology was composed of low grade dysplasia, high grade dysplasia, squamous cell carcinoma (SCC), adenocarcinoma (ADC), others and 10 (2.0 %), 99 (19.5 %), 393 (77.5 %), 4 (0.8%), 1 (0.2 %), respectively. Tumor invasion was classified with m1, m2, m3, sm1, sm2 and 212 (41.8 %), 150 (29.6 %), 78 (15.4 %), 32 (6.3 %), 35 (6.9 %), respectively. Mean location of esophageal neoplasm was 31.0 ± 4.7 cm and it can be divided into cervical esophagus (3, 0.6 %), upper esophagus (40, 7.9 %), middle esophagus (129, 25.4 %) and lower esophagus (326, 64.3 %). Macroscopic superficial type was IIa, IIb, IIc, mixed and 48 (9.5 %), 419 (82.6 %), 29 (5.7 %), 11 (2.2 %), respectively. In case of predominance, left (266, 52,6 %) and right (241, 47.5 %). Circumference was divided into less than 25 %, 25– 50 %, 50– 75 % and more than 75 % and 412 (81.3 %), 76 (15.0 %), 15 (3.0 %) and 4 (0.8 %), respectively. Regarding to direction, transverse was 284 (56.0 %) and longitudinal was 223 (44.0 %). Resected specimen long axis length was 37.7 ± 14.3 mm and tumor long axis length was 22.2 ± 13.7 mm. The injected saline dose was 94.5 ± 69.1 cc. The total procedure time was 46.6 ± 31.0 minutes. Bleeding severity was divided into mild, moderate, severe and 440 (86.8 %), 60 (11.8 %), 7 (1.4 %), respectively. Hemostasis time was 6.7 ± 6.5 minutes. Post–procedure bleeding was

occurred 8 (1.6 %) and stricture needs to ballooning or stent insertion was occurred 14 (2.8 %). Most anesthesia was performed under GA (436, 86.0 %) and the remainder under UCS (71, 14.0 %). Mean platelets were 224 ± 64.2 * 10^3/uL and INR was 1.0 ± 0.1.

Table 1. Baseline characteristics among 454 patients who underwent 507 ESD for esophageal neoplasm

Characteristics	N(%) or mean (SD)
Age (year)	65.2 ± 8.7
Sex (male)	424 (93.4)
Hospitalization (day)	5.2 ± 3.0
Perforation	24 (4.7)
Macroperforation	8 (1.6)
Microperforation	16 (3.2)
History of esophageal ESD	50 (9.9)
Underlying disease	314 (61.9)
Hypertension	152 (30.0)
Diabetes	67 (13.2)
Liver cirrhosis	19 (3.7)
History of Gastric neoplasm	84 (16.6)
Respiratory disease	36 (7.1)
Others	145 (28.6)
Histology	
Low grade dysplasia	10 (2.0)
High grade dysplasia	99 (19.5)
Squamous cell carcinoma	393 (77.5)
Adenocarcinoma	4 (0.8)

Others (spindle cell sarcoma)	1 (0.2)
Invasion depth	
m1 (Epithelial)	212 (41.8)
m2 (Lamina propria)	150 (29.6)
m3 (Muscularis mucosa)	78 (15.4)
sm1 (Extension to submucosa ~200 um)	32 (6.3)
sm2 (Above sm1)	35 (6.9)
Location (upper incision) (cm)	31.0 ± 4.7
Cervical esophagus	3 (0.6)
Upper esophagus	40 (7.9)
Middle esophagus	129 (25.4)
Lower esophagus	326 (64.3)
Type	
Elevated (IIa)	48 (9.5)
Superficial flat (IIb)	419 (82.6)
Depressed (IIc)	29 (5.7)
Mixed	11 (2.2)
Predominance	
Left	266 (52.5)
Right	241 (47.5)
Circumference	
< 25 %	412 (81.3)
25~ 50 %	76 (15.0)
50~ 75 %	15 (3.0)
> 75 %	4 (0.8)
Direction	
Transverse	284 (56.0)
Longitudinal	223 (44.0)
Specimen long axis (mm)	37.7 ± 14.3

Tumor long axis (mm)	22.2 ± 13.7
Normal saline + epinephrine dose (cc)	94.5 ± 69.1
Procedure time (min)	46.6 ± 31.0
Hemostasis time (min)	6.7 ± 6.5
Bleeding severity	
Mild	440 (86.8)
Moderate	60 (11.8)
Severe	7 (1.4)
Other complications	
Postprocedure bleeding	8 (1.6)
Strictures	14 (2.8)
Anesthesia	
Under conscious sedation	71 (14.0)
General anesthesia	436 (86.0)
Platelet (10^3/uL)	224 ± 64.2
INR	1.0 ± 0.1

Characteristics between perforated and non-perforated groups

The clinical characteristics comparison between perforated and non-perforated groups were summarized in Table 2 and perforation sites were described in Figure 1. There was no statistical significant difference in age, sex, underlying disease, histology, invasion depth, location, type, predominance, direction, other complications, anesthesia, platelet and INR between two groups. Hospitalization (10.0 day vs 5.0 day, P<0.0001), circumference (P<0.0001), specimen long axis (44.7 mm vs 37.4 mm, P=0.0131), tumor long axis (27.8 mm vs 21.9 mm, P=0.0257), normal saline + epinephrine dose (144.8 cc vs 92 cc, P=0.0004), procedure time (72.3 min vs 45.3 min, P<0.0001), hemostasis time (9.8 min vs 6.6 min, P=0.0022),

bleeding severity (P=0.0125) were significantly higher in perforated group than non-perforated group.

Table 2. Clinical characteristics comparison between perforated and non-perforated groups

	Perforated group N(%) or mean (SD)	Non-perforated group N(%) or mean (SD)	P-value
Sample size	24	483	
Age (year)	65.7 ± 9.0	65.1 ± 8.7	0.7733
Sex (male)	23 (95.8)	450 (93.2)	>.999
Hospitalization (day)	10.0 ± 7.5	5.0 ± 2.4	<.0001
Perforation			
Macroperforation	8 (34.8)		
Microperforation	16 (66.7)		
History of esophageal ESD	3 (12.5)	47 (9.7)	0.7213
Underlying disease	12 (50.0)	302 (62.5)	0.2174
Hypertension	5 (20.8)	147 (30.4)	0.3163
Diabetes	1 (4.2)	66 (13.7)	0.3474
Liver cirrhosis	1 (4.2)	18 (3.7)	0.6088
History of Gastric neoplasm	4 (16.7)	80 (16.6)	>.999
Respiratory disease	1 (4.2)	35 (7.2)	>.999
Others	4 (16.7)	141 (29.2)	0.185

Histology			0.2627
Low grade dysplasia	0 (0)	10 (2.1)	
High grade dysplasia	1 (4.3)	98 (20.3)	
Squamous cell carcinoma	23 (95.8)	370 (76.6)	
Adenocarcinoma	0 (0)	4 (0.8)	
Others (spindle cell sarcoma)	0 (0)	1 (0.2)	
Invasion depth			0.2175
m1 (Epithelial)	9 (37.5)	203 (42.0)	
m2 (Lamina propria)	7 (29.2)	143 (29.6)	
m3 (Muscularis mucosa)	4 (16.7)	74 (15.3)	
sm1 (Extension to submucosa ~200 um)	4 (16.7)	28 (5.8)	
sm2 (Above sm1)	0 (0)	35 (7.2)	
Location (upper incision) (cm)	31.6 ± 3.7	30.9 ± 4.7	0.4696
Cervical esophagus	0	3 (0.6)	0.4936
Upper esophagus	0	40 (8.3)	
Middle esophagus	7 (30.4)	122 (25.3)	
Lower esophagus	17 (70.8)	309 (64.0)	
Type			0.7712
Elevated (IIa)	1 (4.2)	47 (9.7)	

Superficial flat (IIb)	21 (87.5)	398 (82.4)	
Depressed (IIc)	2 (8.3)	27 (5.6)	
Mixed	0 (0)	11 (2.3)	
Predominance			0.3132
Left	15 (62.5)	251 (52.0)	
Right	9 (37.5)	232 (48.0)	
Circumference			<.0001
< 25 %	7 (29.2)	405 (83.9)	
25~ 50 %	14 (58.3)	62 (12.8)	
50~ 75 %	2 (8.3)	13 (2.7)	
> 75 %	1 (4.2)	3 (0.6)	
Direction			0.134
Transverse	17 (70.8)	267 (55.3)	
Longitudinal	7 (29.2)	216 (44.7)	
Specimen long axis (mm)	44.7 ± 13.5	37.4 ± 14.3	0.0131
Tumor long axis (mm)	27.8 ± 14.5	21.9 ± 13.6	0.0257
Normal saline + epinephrine dose (cc)	144.8 ± 103.3	92.0 ± 66.0	0.0004
Procedure time (min)	72.3 ± 54.0	45.3 ± 28.8	<.0001
Hemostasis time (min)	9.8 ± 7.0	6.6 ± 6.4	0.0022
Bleeding severity			0.0125
Mild	16 (66.7)	424 (87.8)	
Moderate	7 (29.2)	53 (11.0)	

Severe	1 (4.2)	6 (1.2)	
Other complications			0.1825
postprocedure bleeding	0 (0)	8 (1.7)	
Stricture	2 (8.7)	12 (2.5)	
Anesthesia			0.0621
Under conscious sedation	7 (29.2)	64 (13.3)	
General anesthesia	17 (70.8)	419 (86.7)	
Platelet (10^3/uL)	233.0 ± 65.3	223.6 ± 64.2	0.48
INR	1.0 ± 0.1	1.0 ± 0.1	0.7772

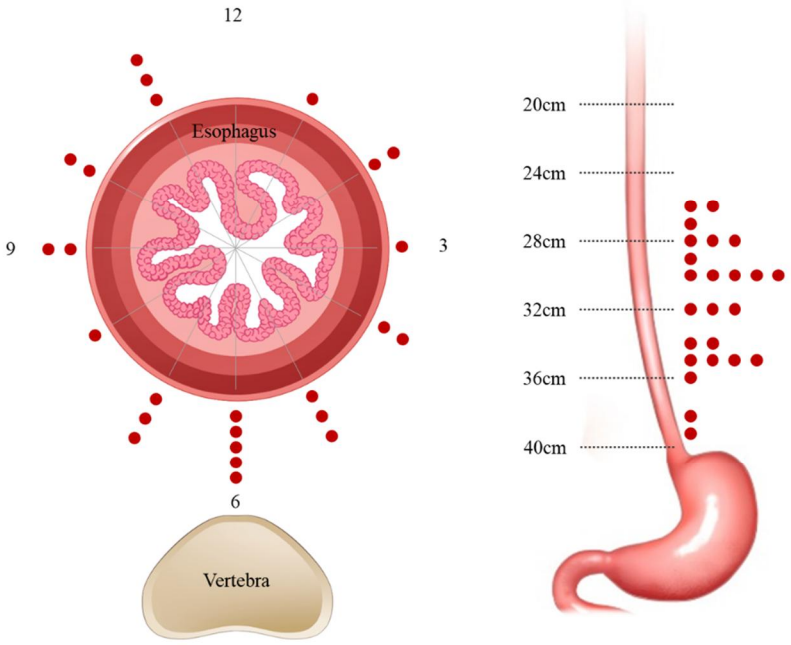

Figure 1. Esophageal ESD perforation sites were described in transverse and longitudinal axis.

Risk factors associated with perforation of esophageal ESD

Circumference (OR=3.669, 95% CI, 2.231- 6.036, P<0.0001), specimen length (OR=1.032, 95% CI, 1.007- 1.058, P=0.013), tumor length (OR=1.027, 95% CI, 1.002- 1.054, P=0.037), normal saline + epinephrine (OR=1.007, 95% CI, 1.002- 1.011, P=0.002), procedure time (OR=1.015, 95% CI, 1.007- 1.024, P<0.001), hemostasis time (OR=1.045, 95% CI, 1.002- 1.090, P=0.04), bleeding severity (OR=2.871, 95% CI, 1.400- 5.890, P=0.004) and anesthesia (OR=2.871, 95% CI, 1.137- 7.250, P=0.026) were risk factors contributing to perforation of esophageal ESD by univariate analysis (Table 3-1). Correlation coefficient of specimen length, tumor length, normal saline + epinephrine, procedure time, hemostasis time, anesthesia, bleeding severity, direction, histology to circumference were 0.398, 0.451, 0.433, 0.457, 0.146, 0.038, 0.216, -0.237, 0.066, respectively. There seems to strong correlation among them, thus specimen length, tumor length, normal saline + epinephrine, procedure time and direction were excluded from multivariate analysis. Table 3-2 shows the result of multivariate analysis. Circumference (OR=3.465, 95% CI, 2.046- 5.955, P<0.001) and UCS (OR=3.861, 95% CI, 1.492- 10.42, P=0.008) was identified as significant risk factors of perforation.

Table 3-1. Risk factors associated with perforation by univariate analysis

	Odds ratio	95% CI	P-value
Age	1.007	0.690- 1.056	0.773
Sex	1.687	0.221- 12.88	0.614
Underlying disease	0.599	0.264- 1.362	0.222
Histology (dysplasia vs cancer)	6.624	0.884- 49.61	0.066

Invasion depth (mucosa vs submucosa)	1.333	0.441– 4.028	0.61
Type	1.163	0.520– 2.602	0.713
Predominance (right vs left)	1.541	0.661– 3.588	0.316
Location	1.033	0.946– 1.129	0.469
Circumference	3.669	2.231– 6.036	<0.001
Direction (transverse vs longitudinal)	0.434	0.168– 1.120	0.085
Specimen length	1.032	1.007– 1.058	0.013
Tumor length	1.027	1.002– 1.054	0.037
Normal saline + epinephrine dose	1.007	1.002– 1.011	0.002
Procedure time	1.015	1.007– 1.024	<0.001
Hemostasis time	1.045	1.002– 1.090	0.04
Bleeding severity	2.871	1.400– 5.890	0.004
Anesthesia (GA vs UCS)	2.871	1.137– 7.250	0.026

Table 3–2. Risk factors associated with perforation by multivariate analysis

	Odds ratio	95% CI	P–value
Circumference	3.465	2.016– 5.955	<0.0001
Hemostasis time	1.025	0.968– 1.084	0.397
Anesthesia (GA vs UCS)	3.861	1.429– 10.42	0.008
Bleeding severity	0.494	0.529– 3.739	0.494
Histology (dysplasia vs cancer)	5.284	0.688– 40.56	0.109

Characteristics comparison between different anesthesia

To compare the efficacy and safety of anesthesia, UCS and GA groups were matched and compared since November 2010. Table 4-1 shows characteristics between two groups, 1:6 matched based on observed covariate (tumor long axis, invasion depth, circumference). There was no significant difference in most factors, and age (66.4 vs 63.6 years, P=0.068) showed a tendency of increasing in UCS. Clinical characteristics comparison was summarized in Table 4-2. Perforation (OR=5.952, 95% CI, 0.365-100.0, P=0.2106) and other complications (OR=0.856, 95% CI, 0.097-7.566, P=0.889) did not show significant difference between two groups. Although bleeding severity (OR=0.601, 95% CI, 0.186- 1.936, P=0.3933) was similar, but hemostasis time (8.2 minutes vs 5.2 minutes, P=0.018) was significantly shorter in GA than UCS. Specimen long axis (26.4 mm vs 31.2 mm, P=0.0157) and hospitalization (4.3 days vs 4.7 days, P=0.0496) were significantly longer in UCS than GA.

Table 4-1. Characteristics of 1:6 matched patients who underwent different anesthesia for ESD

	UCS N(%) or mean (SD)	GA N(%) or mean (SD)	P-value
Sample size	33	192	
Tumor long axis (mm)	14.3 ± 7.6	14.6 ± 7.6	
Invasion depth			
mucosa	28 (84.9)	168 (87.5)	
submucosa	5 (15.1)	24 (12.5)	
Circumference			

< 25 %	33 (100)	192 (100)	
Age (year)	66.4 ± 8.0	63.6 ± 8.2	0.068
Sex (male)	30 (90.9)	175 (91.2)	>0.999
History of esophageal ESD	3 (9.1)	30 (15.6)	0.431
Underlying disease	18 (54.6)	115 (59.9)	0.564
Histology			0.882
Low grade dysplasia	1 (3.0)	6 (3.1)	
High grade dysplasia	9 (27.1)	44 (22.9)	
Squamous cell carcinoma	23 (69.1)	141 (73.4)	
Adenocarcinoma	0	1 (0.52)	
Location (upper incision) (cm)	31.6 ± 4.2	30.8 ± 4.8	0.835
Cervical esophagus	0	2 (1.1)	
Upper esophagus	2 (6.5)	16 (8.5)	
Middle esophagus	6 (19.4)	48 (25.4)	
Lower esophagus	23 (74.2)	123 (65.1)	
Predominance			0.148
Left	12 (36.4)	96 (50)	
Right	21 (63.6)	96 (50)	
Direction			>0.999
Transverse	18 (54.6)	106 (55.2)	
Longitudinal	15 (45.4)	86 (44.8)	
Platelet (10^3/uL)	220.7 ± 60.5	228.0 ± 72.3	0.584
INR	1.0 ± 0.1	1.0 ± 0.1	0.749

Table 4-2. Clinical characteristics associated with different anesthesia

	UCS N(%) or mean (SD)	GA N(%) or mean (SD)	Odds ratio	95% CI	P-value
Hospitalization (day)	4.3 ± 2.3	4.7 ± 2.5			0.0496
Perforation	1 (3.0)	1 (0.5)	5.952	0.365-100.0	0.2106
Microperforation	1 (3.0)	1 (0.5)	5.952	0.365-100.0	0.2106
Specimen long axis (mm)	26.4 ± 10.9	31.2 ± 10.4			0.0157
Normal saline + epinephrine dose (cc)	74.4 ± 43.1	67.5 ± 37.6			0.527
Procedure time (min)	35.8 ± 21.1	33.5 ± 14.4			0.868
Hemostasis time (min)	8.2 ± 10.1	5.5 ± 5.7			0.0181
Bleeding severity			0.601	0.186-1.936	0.3933
Mild	29 (87.9)	177 (92.2)			
Moderate	3 (9.1)	14 (7.3)			
Severe	3 (3.0)	1 (0.5)			
Other complications			0.856	0.097-7.566	0.8885
postprocedure bleeding	0	4 (2.1)			
Stricture	1 (3.0)	1 (0.5)			

Discussion

This study investigated the prevalence and risk factors of esophageal perforation after ESD for esophageal neoplasm and comparative characteristics between GA and UCS. Esophageal perforation has occurred in 4.7 % of esophageal ESD and circumference and UCS were considered to be risk factors of it. In addition, this study suggested that consideration is needed in deciding the type of anesthesia when the circumference of esophageal neoplasm is small. To the best of our knowledge, this is the largest single-center study that demonstrates risk factors of macroperforation and microperforation in esophageal ESD and comparative characteristics between GA and UCS by matching clinical features like a circumference.

There are several previous reports about perforation associated with ESD of gastric cancer or colorectal cancer. Procedure time, invasion depth and location is considered to be risk factors of perforation in gastric cancer. (12-14) Otherwise, tumor size, age, location, and fibrosis is considered to be risk factors of colorectal cancer. (15-17) While the risk factors of post-ESD treatment vary from cancer to cancer, little has been studied for risk factors about the perforation of esophageal ESD. There was a multi-center, large retrospective cohort study based on national administrative database in Japan, but there were no clinicopathologic features such as circumference, location, and histology. (7) Another related study was conducted in Japan, but the subject was limited to 147 patients with early esophageal squamous cell carcinoma and only perforation occurred during the procedure. (18)

In this study, 507 esophageal ESD lesions in 454 patients were compared with the clinicopathologic characteristics. Esophageal perforation was occurred in 24 of 507 (4.7 %) ESD procedures, which is the same rate as previously reported in our center. (8) The perforated group showed

significantly larger circumference and tumor long axis than non-perforated group. It means that the larger size indicates a higher risk of esophageal perforation. Procedure time, bleeding severity, hemostasis time and normal saline + epinephrine dose were also significant, but there was a strong clinical and statistical correlation among them. Tumor invasion depth, type, and histology, as well as patients' age and underlying disease, were not statistically associated with esophageal perforation. Thus, multivariate analysis showed circumference was significant risk factors of esophageal perforation. This result suggests that esophageal perforation of ESD, unlike gastric cancer or colorectal cancer, is associated with neoplasm's size or circumference itself has a greater effect on perforation than tumor's clinicopathologic characteristics or patient's factors. Since the dilatated esophageal wall during insufflation is only 3 to 4 mm, it is thought to be more affected by the size and circumference of the neoplasm itself than gastric cancer or colorectal cancer.

UCS was also another risk factor of esophageal perforation. We performed ESD under UCS mainly at the beginning of the procedure, but after November 2010, most ESD was performed under GA in the operating room. GA is known to have the advantage of shorter treatment time and fewer complications than UCS because dilatated esophageal wall is thin and can easily be affected by the patient's movement or breathing during the procedure. (19) However, at times, ESD was performed under UCS at the decision of the operator, which tended to be the smaller circumference. In fact, GA in all procedures is time-consuming, expensive and it costs a lot of resources such as operating room, nurse and anesthesiologist. (20)

Several studies previously reported that GA was superior to UCS, either reported GA only or simply compared both groups, regardless of size or circumference.(19, 21, 22) Song et al. reported perforation rate was much

lower in GA than in UCS. (21) However, 14.0 % of the perforation rate when using UCS seems much high. To accurately comprehend the effects of anesthesia on perforation related to ESD, consideration should be given to factors that may affect perforation. As mentioned above, UCS tends to be selected when the circumference is small, so the effects on perforation according to the anesthesia type were compared by matching observed covariate (tumor long axis, invasion depth, circumference). According to the analysis, UCS was performed only when the circumference was less than 25 %. Although it was not significant, the older patients tended to be taken UCS and tumor location and histology were not considered.

In a comparison of GA and UCS, perforation and other complications that were known to be superior to UCS was not statistically different. Esophageal perforation only happened one case per each group and effect size is still large, so it is hard to consider there is no difference between the two groups. However, unlike previously reported, the difference in perforation incidence is small, suggesting that UCS may be considered when the circumference is small. In addition, procedure time was also previously reported to be shorter in GA, but there was no significant difference in this study.

Hemostasis time was shorter in GA than in UCS. Although there was no difference in bleeding severity, if bleeding need to control happened, GA is considered advantageous over UCS when bleeding occurs that requires hemostasis. On the other hand, specimen long axis length and hospitalization were longer in GA than in UCS. It is difficult to precisely explain why specimen size is longer in GA than in UCS. It may be because safety margin is wider than in GA than in UCS, or because of operator's preference. Longer hospitalization is thought to be due to small specimen size and the GA itself, which has been reported previously. (22, 23) Van de ven et al. reported that UCS is feasible and safe compared to GA for the ESD of esophageal and

gastric cancer. (10) Given this, it is reasonable to make decision anesthesia method by considering risk and benefit according to the circumference of the lesion rather than selecting GA only in esophageal ESD.

There are several limitations to this study. First, this is a retrospective, observational, and single-center study, so it might limit generalizing the results. Second, six endoscopy specialists performed the procedure and did not take into account their skill or increased proficiency over time. However, it is difficult to calculate the qualitive facts like skills and preference. Third, we only recorded total procedure time, but not closure time when perforation occurred. It can affect the results, but it is excluded from multivariate analysis, so its effect size is quite small. Finally, esophageal perforation by anesthesia method was compared, but the number of case was low. However, unlike previous studies, the incidence of perforation does not differ significantly, suggesting that the UCS would be considered when the circumference is small. More large scale studies are needed to investigate the incidence of perforation by anesthesia method.

Conclusion

In conclusion, this study indicates that the risk factors of esophageal perforation after ESD are circumference and UCS. In addition, if circumference small, in particular, less than 25 %, it is reasonable to determine the anesthesia method by considering the risk and benefit.

References

1. Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, et al. Oesophageal cancer. Nature Reviews Disease Primers. 2017;3:17048.

2. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. The Lancet. 2013;381(9864):400-12.

3. Lao-Sirieix P, Fitzgerald RC. Screening for oesophageal cancer. Nature reviews Clinical oncology. 2012;9(5):278-87.

4. Domper Arnal MJ, Ferrandez Arenas A, Lanas Arbeloa A. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol. 2015;21(26):7933-43.

5. Wani S, Drahos J, Cook MB, Rastogi A, Bansal A, Yen R, et al. Comparison of endoscopic therapies and surgical resection in patients with early esophageal cancer: a population-based study. Gastrointest Endosc. 2014;79(2):224-32.e1.

6. Hammad H, Kaltenbach T, Soetikno R. Endoscopic Submucosal Dissection for Malignant Esophageal Lesions. Current Gastroenterology Reports. 2014;16(5):386.

7. Odagiri H, Yasunaga H, Matsui H, Matsui S, Fushimi K, Kaise M. Hospital volume and adverse events following esophageal endoscopic submucosal dissection in Japan. Endoscopy. 2017;49(4):321-6.

8. Park H, Kim DH, Gong EJ, Na HK, Ahn JY, Lee JH, et al. Ten year experience of esophageal endoscopic submucosal dissection of superficial esophageal neoplasms in a single center. J Clin Oncol. 2016;34(4).

9. Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. Clin Gastroenterol H. 2006;4(6):688-94.

10. van de Ven S, Leliveld L, Klimek M, Hilkemeijer T, Bruno MJ, Koch AD. Propofol sedation without endotracheal intubation is safe for endoscopic

submucosal dissection in the esophagus and stomach. United European Gastroenterol J. 2019;7(3):405-11.

11. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon - November 30 to December 1, 2002. Gastrointest Endosc. 2003;58(6):S3-S43.

12. Biancari F, D'Andrea V, Paone R, Di Marco C, Savino G, Koivukangas V, et al. Current Treatment and Outcome of Esophageal Perforations in Adults: Systematic Review and Meta-Analysis of 75 Studies. World J Surg. 2013;37(5):1051-9.

13. Ota M, Nakamura T, Hayashi K, Ohki T, Narumiya K, Sato T, et al. Usefulness of clip traction in the early phase of esophageal endoscopic submucosal dissection. Digest Endosc. 2012;24(5):315-8.

14. Yoo JH, Shin SJ, Lee KM, Choi JM, Wi JO, Kim DH, et al. Risk factors for perforations associated with endoscopic submucosal dissection in gastric lesions: emphasis on perforation type. Surg Endosc. 2012;26(9):2456-64.

15. De Ceglie A, Hassan C, Mangiavillano B, Matsuda T, Saito Y, Ridola L, et al. Endoscopic mucosal resection and endoscopic submucosal dissection for colorectal lesions: A systematic review. Crit Rev Oncol Hemat. 2016;104:138-55.

16. Kim ES, Cho KB, Park KS, Lee KI, Jang BK, Chung WJ, et al. Factors predictive of perforation during endoscopic submucosal dissection for the treatment of colorectal tumors. Endoscopy. 2011;43(7):573-8.

17. Lee EJ, Lee JB, Lee SH, Youk EG. Endoscopic treatment of large colorectal tumors: comparison of endoscopic mucosal resection, endoscopic mucosal resection-precutting, and endoscopic submucosal dissection. Surg Endosc. 2012;26(8):2220-30.

18. Noguchi M, Yano T, Kato T, Kadota T, Imajoh M, Morimoto H, et al. Risk factors for intraoperative perforation during endoscopic submucosal dissection of superficial esophageal squamous cell carcinoma. World J

Gastroentero. 2017;23(3):478-85.
19. Hamada K, Kawano K, Yamauchi A, Koyanagi R, Horikawa Y, Nishida S, et al. Efficacy of Endoscopic Submucosal Dissection of Esophageal Neoplasms under General Anesthesia. Clin Endosc. 2019;52(3):252-7.
20. Rong QH, Zhao GL, Xie JP, Wang LX. Feasibility and safety of endoscopic submucosal dissection of esophageal or gastric carcinomas under general anesthesia. Med Princ Pract. 2013;22(3):280-4.
21. Song BG, Min YW, Cha RR, Lee H, Min BH, Lee JH, et al. Endoscopic submucosal dissection under general anesthesia for superficial esophageal squamous cell carcinoma is associated with better clinical outcomes. BMC Gastroenterol. 2018;18(1):80.
22. Yamashita K, Shiwaku H, Ohmiya T, Shimaoka H, Okada H, Nakashima R, et al. Efficacy and safety of endoscopic submucosal dissection under general anesthesia. World J Gastrointest Endosc. 2016;8(13):466-71.
23. Yurtlu DA, Aslan F, Ayvat P, Isik Y, Karakus N, Unsal B, et al. Propofol-Based Sedation Versus General Anesthesia for Endoscopic Submucosal Dissection. Medicine (Baltimore). 2016;95(20):e3680.

국문요약

목적: 식도 종양에 대해 시행한 내시경적 점막하 절제술과 관련하여 천공의 유병률과 위험인자, 그리고 어떤 마취 방법이 적절한지에 대해 알아보고자 한다.

방법: 2007년 10월부터 2019년 2월까지 507건의 서울아산병원에서 시행한 식도 종양에 대한 내시경적 점막하 절제술을 후향적으로 분석하였다. 시술과 관련된 천공의 위험인자를 분석하기 위해 이원 로지스틱 회귀분석과 다변량 분석을 이용했다. 마취방법에 따른 천공의 차이를 알아보기 위해 전신마취를 본격적으로 시작한 2010년 11월 이후 천공에 영향을 미칠 수 있는 공변량 (종양의 장축, 침습 깊이, 둘레)을 1:6 매칭하여 의식하 진정과 전신마취군을 비교했다. 매칭된 쌍은 일반화 추정 방정식, 선형 복합 모델을 이용하여 결과 분석을 하였다.

결과: 식도 종양에 대해 시행한 내시경적 점막하 절제술 507건 중 24건 (4.7 %)에서 천공이 발생하였다. 모든 기간 시행한 시술을 분석했을 때, 의식하 진정(OR= 3.861, 95% CI, 1.429– 10.42, P=0.008)과 식도에서 식도종양이 차지하는 비율이 클수록 (OR=3.465, 95% CI, 2.046– 5.955, P<0.001) 천공의 위험이 커졌다. 나이(OR=1.007, 95% CI, 0.690– 1.056, P=0.773), 성별(OR=1.687, 95% CI, 0.221– 12.88, P=0.614), 기저 질환(OR=0.599, 95% CI, 0.264– 1.362, P=0.222), 침윤 깊이(OR=1.333, 95% CI, 0.441– 4.023, P=0.61), 조직학적 소견(OR=6.624, 95% CI, 0.884– 49.61, P=0.066), 병변 주요 위치(OR=1.541, 95% CI, 0.661– 3.588, P=0.316), 종축 위치(OR=1.033, 95% CI, 0.946– 1.129, P=0.469), 방향(OR=0.434, 95% CI, 0.168– 1.120, P=0.085)은 유의하지 않았다.

하지만 본격적으로 전신마취를 시작한 이후 마취 방법에 따라 비교했을 때 둘레가 25 % 미만인 경우 천공 (OR=5.952, 95% CI, 0.365– 100.0, P=0.2106)과 기타 합병증 (OR=0.856, 95% CI, 0.097– 7.566, P=0.889)에서 유의미한 통계적 차이가 없었다.

결론: 둘레가 큰 것과 의식하 진정이 식도 종양에 대한 내시경적 점막하 절제술

천공의 위험인자로 생각된다. 하지만 천공에 영향을 미치는 요인을 고려하여 비교했을 때 식도 종양의 둘레가 25 % 미만일 때 마취 방법에 따른 식도 천공의 차이 (OR=5.952, 95% CI, 0.365– 100.0, P=0.2106)가 없었다. 그러므로 식도 종양의 크기에 따라 마취방법을 선택하는 것이 합리적으로 생각된다.

키워드: 식도 종양, 내시경적 점막하 절제술, 천공, 위험 인자, 마취