

Injury to the Muscle Layer and Risk of Non-cardiac Chest Pain after Endoscopic Submucosal Dissection for Esophageal Cancer

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ABSTRACT

Background & Aims: Non-cardiac chest pain (NCCP) is a frequent complication of endoscopic submucosal dissection (ESD) for early-stage esophageal cancer. However, little is known about relationships between ESD findings and NCCP. This study aims to evaluate the risk factors for NCCP, including ESD findings related to injury to the muscle layer.

Methods: We enrolled a total of 296 lesions from 270 patients with esophageal squamous cell carcinoma (ESCC), who underwent ESD in our center. The grade of injury to the muscle layer caused by ESD was categorized as follows: grade 0: no exposure of muscularis propria; grade 1: muscularis propria exposure and/or whitish color change by the electrocoagulation; grade 2: torn muscularis propria with whitish color change by the electrocoagulation; and grade 3, esophageal perforation. The risk factors for NCCP, including ESD findings, were analyzed by univariate and multivariate analyses.

Results: NCCP occurred in 89 patients (33.0%) after esophageal ESD. Multivariate analysis demonstrated that younger age [odds ratio (OR) 0.95, 95% confidence interval (95%CI) 0.92-0.98, $p=0.003$], postoperative fever ($\geq 38^{\circ}\text{C}$) (OR=25.9, 95%CI: 2.89-232.10, $p=0.004$), ESD findings (grade 1: OR=3.99, 95%CI: 1.63-9.75, $p=0.003$ and grade 2: OR=3.18, 95%CI: 1.54-6.57, $p=0.002$) were independently associated with the incidence of post ESD NCCP.

Conclusions: ESD findings relate to slight injury to the muscle layer, such as muscularis propria exposure and whitish color change by the electrocoagulation were identified as risk factor for post ESD NCCP. We should therefore perform esophageal ESD carefully to avoid injuring the muscle layers.

Key words: non-cardiac chest pain – endoscopic submucosal dissection – early-stage esophageal cancer – ESD findings – esophageal squamous cell carcinoma.

Abbreviations: EMR: endoscopic mucosal resection; ESCC: esophageal squamous cell carcinoma; ESD: endoscopic submucosal dissection; NCCP: non-cardiac chest pain; NRS: numerical rating scale; PEECS: post-ESD electrocoagulation syndrome; WBC: white blood cells.

INTRODUCTION

Endoscopic submucosal dissection (ESD) is an effective and minimally invasive treatment for early-stage esophageal cancer [1-3]. With the wide application of this procedure, much more attention has been paid to the ESD-related complications. Postoperative complications of esophageal ESD include bleeding, aspiration pneumonia, stenosis, and pain [4]. Among them, non-cardiac chest pain (NCCP) is

often experienced in patients undergoing esophageal ESD after the procedure [5-7]. Because postoperative pain causes both mental and physical distress to patients, understanding the related factors that influence post-ESD pain would provide useful information for the physician regarding individual risk factors for pain. It has been reported that patients with distal gastric lesions and those with dyspepsia were more likely to develop postoperative pain after gastric ESD [8]. In the colorectal ESD, postoperative pain was related to postoperative electrocoagulation syndrome, a complication following ESD [9, 10]. Recent studies on esophageal ESD identified several factors associated with post ESD NCCP, such as postoperative elevation of white blood cells (WBC), fever, and history of previous surgery [6, 7]. However, information that can predict NCCP before or during ESD procedure is still limiting. Therefore, we

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attempted to focus on the ESD finding during the procedure, such as the appearance of ESD ulcer to better predict NCCP after esophageal ESD. In this study, we investigated the association between risk factors including ESD findings related to injury to the muscle layer and incidence of NCCP after esophageal ESD.

METHODS

Study Subjects

We studied 296 early stage esophageal squamous-cell carcinoma (ESCC) lesions from 270 patients who underwent ESD treatment in the Department of Gastroenterology, Kansai Medical University Hospital, from February 2007 to November 2022. Indications for ESD were ESCC with a clinical invasion depth of T1a or T1b-SM1 (200 μ m from the muscularis mucosa). Demographic data and clinicopathologic features including patient age, gender, location, morphology, size and invasion depth of the lesion, systemic inflammatory response markers within 24 hours after ESD (e.g., white blood cell [WBC] count, C-reactive protein [CRP], and body temperature) was obtained based on the medical record. Location, and invasion depth of the lesion was assigned according to the Japanese Classification of Esophageal Cancer, 11th Edition [11]. We excluded cases whose post-operative pathology was not ESCC, cases with combined gastric, duodenal, and/or colonic lesions that required simultaneous endoscopic treatment, and patients who underwent simultaneous endoscopic mucosal resection (EMR) for esophageal lesion. The study was conducted in accordance with the ethical principles included in the Declaration of Helsinki and the study protocol was approved from the institutional review board (ID: 2021235). A written informed consent was obtained from all patients.

ESD Procedure

Endoscopic submucosal dissection was performed following standard procedures. A tip attachment (D-201-

11304; Olympus, Tokyo, Japan) was mounted on an endoscope (GIF-260J, H260Z and H290Z; Olympus), and ESD knives (IT-nano, and Dual knife; Olympus) and a high-frequency electrosurgical system (VIO-200D; Erbe, Tübingen, Germany) were used. The high-frequency settings were set to ENDO CUT I Effect 1 for mucosal incision and to Swift Coag Effect 3, 30 W for submucosal dissection. Endoscopic submucosal dissection was performed in the endoscopy room with the patient under local anesthesia by regular intravenous administration of midazolam or in the operating theater with the patient under general anesthesia using carbon dioxide. The lesions were marked following iodine staining, and a mixed injection of 0.4% sodium hyaluronate solution (MucoUp, Seikagaku Corp., Tokyo, Japan) added to a saline or glycerol solution with a small quantity of indigo carmine was used as a local injection. After ESD, the patients were closely observed to detect any adverse events. Intravenous proton pump inhibitors were administered to prevent procedure-related bleeding. Chest and abdominal X-rays were taken immediately at the end of the procedure and the following morning to identify any leakage of luminal air or pneumonic consolidation. If any aspiration or minute perforation was suspected during ESD, CT scanning was performed, and prophylactic antibiotics were administered to the patients.

Assessment of Post ESD NCCP and ESD Findings

Presence of NCCP in the 24 hours post-ESD was evaluated using the numerical rating scale (NRS) [12]. Non-cardiac chest pain with a NRS ≥ 4 point was assigned to the NCCP positive group. During the ESD procedure, post-ESD ulcer was carefully observed and the grade of injury to the muscle layer caused by ESD was categorized as follows: grade 0: no exposure of muscularis propria; grade 1: muscularis propria exposure and/or whitish color change by the electrocoagulation; grade 2: torn muscularis propria with whitish color change by the electrocoagulation; and grade 3: esophageal perforation (Fig.1).

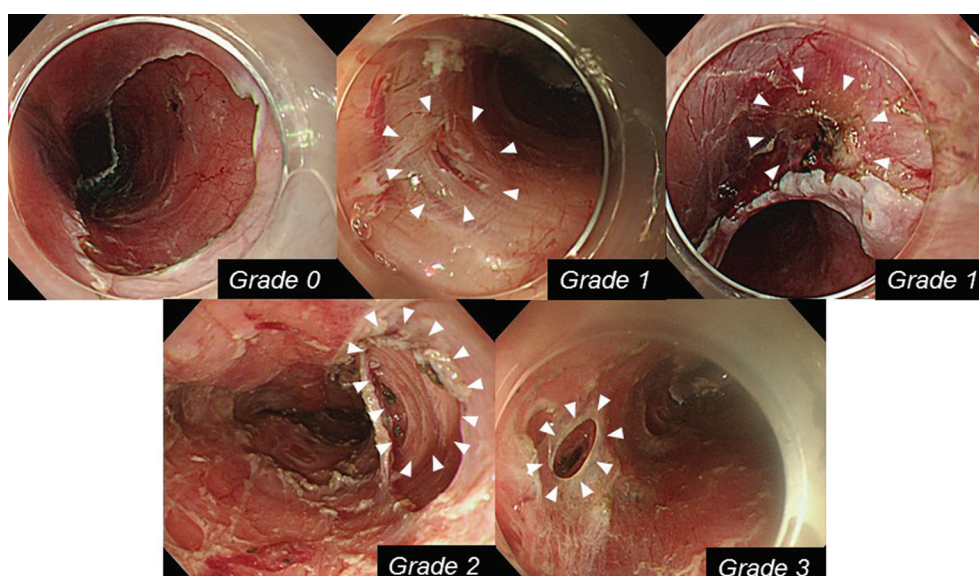


Fig. 1. Assessment of ESD findings after esophageal ESD. Grade 0: no exposure of muscularis propria. Grade 1: muscularis propria exposure and/or whitish color change by the electrocoagulation (white arrow heads). Grade 2: torn muscularis propria with whitish color change by the electrocoagulation (white arrow heads). Grade: 3: esophageal perforation (white arrow heads).

Assessment of endoscopic findings was based on the stored images and interpretation was performed by the consensus manner by the two expert endoscopists (T.T. and T.S.) in order to evaluate their reasonability. If their opinions did not agree, a final judgment was arrived by consensus following the discussion of each individual cases.

Statistical Analysis

The risk factors for post-ESD NCCP, including injury to the muscle layer, were analyzed by univariate and multivariate analyses. The odds ratios (OR) and 95% confidence intervals (CI) were also calculated by logistic regression with adjustment for factors associated with post-ESD NCCP. A probability value of less than 0.05 was considered statistically significant in all analyses.

RESULTS

Clinicopathological characteristics of 296 ESCC lesions from 270 patients are summarized in the Table I. Out of 270 patients who underwent esophageal ESD, post-ESD NCCP occurred in 89 patients (33.0%) after ESD. Regarding the ESD findings of post-ESD ulcer, 179 (66.3%), 29 (10.7%), 54 (20.0%) and 8 (2.9%) were classified as grades 0, 1, 2, 3, respectively. Initially, we investigated the association between clinicopathological factors and incidence of NCCP by the univariate analyses. Gender, age, lesion size and depth, number of ESD, ESD findings, WBC count, C reactive protein (CRP), body temperature, presence of aspiration pneumonia and mediastinal emphysema were included for this analysis. The result demonstrated that that younger age ($p=0.01$), larger lesions size ($p=0.009$), depth of lesion (sm2: $p<0.05$), multiple ESD ($p=0.008$), higher WBC count ($p=0.007$), higher CRP ($p=0.01$), postoperative fever (37.0°C - 37.9°C : $p=0.02$; $\geq 38.0^{\circ}\text{C}$: $p=0.005$), presence of mediastinal emphysema ($p=0.02$), and ESD findings (grade 1: $p=0.008$, grade 2: $P<0.0001$) were statistically associated with the incidence of post ESD NCCP (Table II). We then performed multivariate analysis for adjustment for statistically significant risk factors. This analysis demonstrated that younger age [odds ratio (OR): 0.95, 95% confidence interval (95%CI): 0.92-0.98, $p=0.003$],

postoperative fever ($>38.0^{\circ}\text{C}$) (OR=25.90, 95%CI: 2.89-232.10, $p=0.004$), ESD findings (grade 1: OR=3.99, 95%CI: 1.63-9.75, $p=0.003$, grade 2: OR 3.18, 95%CI: 1.54-6.57, $p=0.002$) were independently associated with the incidence of post ESD NCCP (Table III).

DISCUSSION

The present study evaluated the risk factors for NCCP, including detailed ESD findings. We have shown that age, postoperative fever, ESD findings were independently associated with the incidence of post ESD NCCP. Although NCCP is often experienced in patients undergoing esophageal ESD [6, 7], information that can predict NCCP before or during ESD procedure have been limited. Our result provided evidence that the risk of NCCP can be predicted by the ESD findings during the procedure.

Table II. Univariate analysis assessing factors associated with NCCP

Variables	NCCP (-)	NCCP (+)	p
Gender			
Female	28	21	Reference
Male	153	68	0.11
Age: median (range)	71.8 (66-90)	70.6 (45-87)	0.01
Lesion size: median (range)	14.0 (2-65)	20.0 (3-64)	0.009
Depth			
EP-LPM	158	67	Reference
MM-SM1	22	18	0.06
SM2	1	4	<0.05
Number of ESD			
Single ESD	171	75	Reference
Multiple ESD	10	14	0.008
ESD findings			
Grade 0	136	43	Reference
Grade 1	15	14	0.008
Grade 2	25	29	<0.0001
Grade 3	5	3	0.39
WBC count (x100 /mm ³): mean+/- SEM	87.0+/-1.91	99.6+/-2.99	0.007
CRP (mg/dL): mean+/- SEM	1.12+/-0.08	1.64+/-0.21	0.01
Body Temperature			
<37°C	158	12	Reference
37°C-37.9°C	22	19	0.02
$\geq 38^{\circ}\text{C}$	1	8	0.005
Aspiration pneumonia			
Absent	178	86	Reference
Present	3	3	0.38
Mediastinal emphysema			
Absent	177	81	Reference
Present	4	8	0.02

Significant results were indicated by the bold characters. ESD: endoscopic submucosal dissection; NCCP: non cardiac chest pain; CRP: C reactive protein; WBC: white blood cells. For the rest of abbreviations see Table I.

Table I. Study cohort

Variables	
Number of patients	270
Number of lesions	296
Age: median (range)	71.1 (45-90)
Gender: male/ female	221/49
Location: Ce/Ut/Mt/Lt/Ae	5/15/222/42/12
Morphology: Elevated/ Depressed/ Flat	11/194/91
Size (mm): median (range)	14 (2-65)
Depth: EP-LPM/ MM-SM1/ SM2	251/40/5

Ce: Cervical esophagus; Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; LT: lower thoracic esophagus; Ae: abdominal esophagus; EP/ LPM: tumor limited to the epithelium or lamina propria mucosa; MM/ SM1: tumor invading the muscularis mucosae or submucosa to a depth of 200 μm or less from the muscularis mucosae; SM2: tumor invading the submucosa to a depth of more than 200 μm .

Table III. Multivariate analysis assessing factors associated with NCCP

Variables	OR (95%CI), p
Age: median (range)	0.95 (0.92-0.98), 0.003
Lesion size: median (range)	1.01 (0.98-1.03), 0.62
Depth	
EP-LPM	Reference
MM-SM1	6.97 (0.66-7.32) 0.16
SM2	1.72 (0.77-3.87) 0.11
Number of ESD	
Single ESD	Reference
Multiple ESD	2.15 (0.75-6.14) 0.15
ESD findings	
Grade 0	Reference
Grade 1	3.99 (1.63-9.75) 0.003
Grade 2	3.18 (1.54-6.57) 0.002
Grade 3	0.84 (0.12-5.97) 0.86
WBC count (x100 /mm3)	1.01 (0.99-1.02) 0.10
CRP (mg/dL)	1.02 (0.80-1.30) 0.87
Body Temperature	
<37°C	Reference
37°C-37.9°C	1.72 (0.77-3.87) 0.19
>=38°C	25.90 (2.89-232.10) 0.004
Mediastinal emphysema	
Absent	Reference
Present	3.63 (0.74-1.77) 0.11

Significant results were indicated by the bold characters. For abbreviations see Tables I and II.

Regarding the association between NCCP and risk factors, different associations were generated in other previous studies. Sakai et al. [6] reported that elevation of WBC count on post-operative day 1 was independently associated with chest pain after esophageal ESD, while the ESD findings such as muscle layer exposure was not associated with the incidence of chest pain. Other study by Zhao et al. [7] showed that postoperative fever and history of previous surgery were independent risk factors for chest pain after esophageal ESD, while use of titanium clips due to muscle layer injuries was not the factor associated with the chest pain. Discrepancies between other studies and our study might be due to the patients' constitution and difference in definition of ESD findings. Results from the study of Sakai et al. [6] were based on a relatively small sample size (n=42), which may underestimate influence of risk factor associated with NCCP including ESD findings. Zhao et al. [7] investigated the association between NCCP and use of titanium clips for muscle layer injuries. But this study did not evaluate the detailed findings of post ESD ulcer which may be the reason for negative association between NCCP and ESD findings. In the present study, findings of post ESD ulcer was divided into four categories (grades 0 to 3) according to the grade of injury to the muscle layer. The positive association between grades 1 and 2 with the incidence of NCCP emphasizes the importance of careful observation of ESD findings to predict the risk of NCCP.

Concerning the degree of injury to the muscle layer, grades 2 and 3 are characterized as more severe injury to the muscle layer caused by ESD, compared to grade 1. However, we did not observe significant association between Grade 3, which represents most severe injury to the muscle layer, and NCCP, possibly due to the rare frequency of this category. On the other hand, in addition to the grade 2, grade 1 lesions, which represents a slight injury to the muscle layer were identified as an independent risk factor for NCCP. Potential association between such minute injury to the muscle layer and incidence of NCCP can be explained by the unique anatomical character of the esophagus which lacks a serosa. Heat by high-frequency devices can be more easily transmitted to deeper layer of the esophageal rumen leading to the NCCP. We should therefore perform esophageal ESD carefully to avoid injuring the muscle layers.

We have shown that fever ($\geq 38^{\circ}\text{C}$) was also independently associated with the incidence of NCCP, which was in line with other study [6]. Postoperative fever has been considered as a part of symptom of post-ESD electrocoagulation syndrome (PEECS) [5], a complication following ESD. Since PEECS leads to fever and abdominal pain as a result of serosal burns or transmural burns during endoscopic treatment by high-frequency devices, it is therefore reasonable to expect the positive association between postoperative fever and incidence of NCCP. However, fever itself is post-operative symptom, being less useful to predict NCCP before or during ESD procedure. We have also shown that age was an independent factor associated with the incidence of post ESD NCCP. The result suggest that older age was less risk for post ESD NCCP. The result may be explained by the age difference in pain sensitivity. In general, older adults in comparison to young adults, show an overall increase in pain thresholds, reflecting a decline in pain sensitivity [13]. This issue may be also applicable to our result, suggesting that younger patients are more susceptible to develop post ESD NCCP.

Since age and ESD findings are the factors that can predict NCCP before or during ESD procedure, these factors would be useful for the physician to perform better implementation reflecting individual risk for pain. One indicates that muscle layer injury should be avoided during the ESD. Our result also opened the avenue for the appropriate individual implementation reflecting the risk for chest pain based on the endoscopic finding. For patients who is high risk for chest pain, active use of analgesic medication can be considered.

A limitation of our study is represented by the retrospective analysis on a cohort from a single center. Further case accumulation will be needed to confirm our result. However, our study provided first evidence that the careful observation of ESD findings is useful to predict NCCP after esophageal ESD. We expect that our result provides salient findings despite its limitation.

CONCLUSIONS

Endoscopic submucosal dissection findings related to a slight injury to the muscle layer, such as muscularis propria exposure and whitish color change by the electrocoagulation were identified as risk factor for post ESD NCCP. We should

therefore perform esophageal ESD carefully to avoid injuring the muscle layers.

Conflicts of interest: None to declare.

Authors' contribution: T.T. and T.S. conceived and designed the study. T.T. and T.S. analysed the data and drafted the manuscript. S.N., S.K., Y.M., N.N. and Y.T. interpreted the results and revised the manuscript. T.O., T.T., Y.H., N.F., T.F and M.N. supervised the project and revised the manuscript for its scientific content. All the authors approved the final version of the manuscript.

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