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Reasonable decision of anesthesia methods in patients who underwent endoscopic submucosal dissection for superficial esophageal carcinoma: A retrospective analysis in a single Japanese institution

ESOPHAGUS

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Original Article

ABSTRACT

Background/Aims: Despite being a valuable therapeutic option, it has not yet been reported whether endoscopic submucosal dissection (ESD) for superficial esophageal carcinoma should be performed under general or non-general anesthesia (sedation).

Materials and Methods: The clinicopathological factors (age, sex, histology, tumor size, tumor location, tumor macroscopic morphology, and adverse events) of 110 superficial esophageal carcinoma lesions (98 patients) treated by ESD at a single Japanese institution from January 2007 to December 2013 were retrospectively reviewed using medical records.

Results: Among 110 lesions, 94 lesions were resected under general anesthesia, and 16 lesions were resected under non-general anesthesia by an experienced endoscopist. Although the number of complications was 12 in the group of general anesthesia and 1 in sedated patients, no significant differences between both groups were found in the incidence of adverse events (total adverse events: 12.2% versus 1.02%, p=0.456; mediastinal emphysema: 11.2% versus 1.02%, p=0.518; pulmonary atelectasis: 1.02% versus 0%, p=0.679). All of the events could be managed conservatively.

Conclusion: For ordered management of accidental events during esophageal ESD, general anesthesia might be a crucial option for a better clinical outcome even when administered by non-experienced operators.

Keywords: Endoscopic submucosal dissection, superficial esophageal carcinoma, adverse event, general anesthesia, non-general anesthesia

INTRODUCTION

Although the incidence of squamous cell carcinoma (SCC) has decreased marginally in Western countries (1), SCC accounts for 95% of all esophageal carcinomas in Japan (2,3). A poor survival rate of 20% in patients with local esophageal cancer has been demonstrated, even after aggressive therapy such as surgical resection, chemoradiation, or their combination (4,5).

On the other hand, when this cancer is detected at an early stage, it can be cured by endoscopic treatment. Endoscopic mucosal resection (EMR) was widely performed as an alternative to surgical treatment for patients with node-negative esophageal cancer. EMR provides reliable histological staging using depth of invasion, lymphatic-vascular involvement, and neoplastic margins during therapy (6). In addition, EMR has been shown to be a safer alternative if the depth of this disease is limited to the esophageal mucosa, with less invasive treatment, organ preservation, and similar long-term outcomes as those achieved with surgery (7,8). However, with EMR, en bloc resection of lesions larger than 2 cm is extremely difficult. It is well known clinically that the local recurrence rate after piecemeal resection is higher than en bloc resection (9-11). Endoscopic submucosal dissection (ESD) was developed for early gastric cancer to obtain en bloc material while causing less local recurrent disease (12,13). Despite the technical difficulties (14), ESD enables the operator to achieve an en bloc resection regardless of the tumor size for esophageal and colorectal neoplasia (15).

From a technical point of view, ESD for esophageal lesions seems to be a demanding procedure even for ESD-dedicated endoscopists. Complications of esophageal ESD typically include perforations, mediastinal

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emphysema, subcutaneous emphysema, and aspiration pneumonia. This is because the esophageal wall is thinner than the stomach and moves with respiration and heartbeat in a narrow space, causing difficult maneuverability of devices. Therefore, intubation and general anesthesia might be preferable for an ESD procedure that is expected to be time-consuming.

Because there was no report regarding the recommended adequate anesthesia methods during esophageal ESD, to clarify the present status, we retrospectively investigated ESD for superficial esophageal carcinoma performed under general or non-general anesthesia in a single Japanese institution.

MATERIALS AND METHODS

Patients

From January 2007 to December 2013, 151 consecutive patients (170 lesions) who provided written informed consent underwent endoscopic resection for esophageal carcinoma at Tokyo Medical University Hospital. The methods of endoscopic resection were decided based on tumor size, namely, EMR for lesions <1 cm in diameter and ESD for lesions ≥1 cm in diameter. Of these 170 endoscopically-treated lesions, we compared general sedation and non-general anesthesia in ESD for 110 superficial esophageal carcinoma lesions (98 patients). Among them, the clinicopathological factors [age; sex; daily habits, including smoking and drinking; comorbidities, including esophageal hiatal hernia and Barrett's esophagus; histology; tumor depth; tumor size; tumor location; tumor macroscopic morphology (16); and adverse events] during endoscopic resection were retrospectively compared according to the anesthesia methods using medical records. All ESDs under non-general anesthesia were performed by an expert operator who has more than 50 esophageal ESD or non-experts under expert supervision.

In this study, we excluded particular histopathological types (special variants of esophageal carcinoma, basaloid cell carcinoma, anaplastic carcinoma, and adenosquamous carcinoma) because the consensus for endoscopic resection in these cases has not been established. All patients agreed after explanation of the risks and benefits of ESD, including complication of the endoscopic treatment and possibility of additional surgical treatment if necessary. Although the ethics committee approval was not presented because all procedures were performed as routine clinical practice, written Informed consent before each endoscopic procedure and an all-inclusive agreement form was obtained as per the institutional protocol from all patients.

Endoscopic resection

Endoscopic resection was indicated for superficial esophageal carcinoma without an ulcer or obvious protrusion, suggesting invasion to a deeper part of the submucosal layer. Patients were treated according to the 2007 Japan Esophageal Society guidelines for the treatment of esophageal cancer (17), Endoscopic resection was performed with carbon dioxide (CO_2) insufflation on a patient under non-general anesthesia by periodic intravenous administration of midazolam in an endoscopic room or under general anesthesia in an operating theater.

ESD was performed according to standard steps using specially designed knives, including the IT-2, IT-nano, and Dual knife (Olympus Medical Systems). A high-frequency surgical generator with an automatically controlled system (ESG-100, Olympus Medical Systems or VIO-300D; Erbe, Tübingen, Germany) was used.

Lugol chromoendoscopy was performed before marking the lateral margin of the lesion, which could be visualized as the border between the stained and unstained areas. Because the muscularis propria of the esophageal wall is thinner than that of the gastric wall and is always in motion with the heartbeat, sufficient space should be secured between the mucosa and muscularis propria through submucosal injection with 0.4% sodium hyaluronate solution (MucoUp, Seikagaku Corp.; Tokyo, Japan) (18).

Conscious sedation and general anesthesia methods

All patients enrolled in this study were assessed by the American Society of Anesthesiologists (ASA) (19) physical status class. In the cases under general anesthesia, propofol was administered at 1–2 mg/kg/min intravenously for induction. Rocuronium was administered at 0.6–0.9 mg/kg as a muscle relaxant in addition to the administration of 3% sevoflurane during tracheal intubation. We maintained sevoflurane at 1%–1.5% during surgery. We also administered remifentanil at 0.3–0.5 μg/kg/min as an adjunct to anesthesia.

In the group under non-general anesthesia, the initial bolus of 3 mg of midazolam (Astellas Pharma Inc.; Tokyo, Japan) for patients of body weight <50 kg or 4 mg of midazolam for patients of body weight ≥50 kg was administered through an intravenous catheter. Incremental doses of midazolam (2 mg) were administered if the patient showed signs of discomfort, restlessness, or agitation or responded to verbal commands. All patients received 15 mg of pentazocine as an analgesic agent at the start of ESD and at 60-min intervals thereafter during the procedure. All medications were administered by a gastroenterologist who did not participate directly in the esophageal ESD procedures. At least one physician with advanced training in basic and cardiac life support was present during every ESD procedure. Patients received supplemental oxygen (2 L/min) by nasal cannula in the endoscopy room as their vital signs and oxygen saturation were continuously monitored and recorded every 5 mins using a standard three-lead electrocardiogram, pulse oximetry, and automatic blood pressure equipment. Chest excursion and respiratory rates were monitored visually.

Adverse events

Bleeding related to the procedure was defined as bleeding that required hemostatic treatment, such as coagulation or endo-

scopic clipping. Perforation was diagnosed when the mediastinal connective tissue was observed during the procedure. Muscle damage was defined as scratching and/or rupture of muscle fibers on reviewing endoscopic images. Mediastinal emphysema was diagnosed based on the presence of air in the mediastinal space on plain radiography. A postoperative stricture was defined as a stricture that required endoscopic treatment.

Statistical analysis

Data management and statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS) software version 22 (IBM; Chicago, IL, USA). Quantitative data were compared using the Mann–Whitney U-test. For categorical variables, the Fisher's exact test or Chi-square test was used. Statistically significant variables in the univariate analysis were entered into multivariate logistic regression analysis. Odds ratios with 95% confidence intervals (95% CIs) quantified the extent of the association. A value of $p<0.05$ was considered significant for all tests.

RESULTS

Baseline characteristics of the subject

Among 151 patients, ESD was performed in 98 patients (65.0%), and EMR was performed in 53 patients (35.1%). There were significant differences in tumor size and gross classification between ESD and EMR. All EMRs were performed under non-general anesthesia. However, four patients underwent both ESD and EMR under general anesthesia; in these patients, EMR was performed during ESD to remove synchronous multiple lesions. The invasion depth was EP/LPM in 126 patients, MM in 24, SM1 in 6, SM2 in 13, and MP in 1 (Table 1,2).

Clinicopathological factors between general and non-general anesthesia

We compared the baseline clinicopathological factors between general and non-general anesthesia performed for 110 superficial esophageal carcinoma lesions (98 patients) treated with ESD. General and non-general anesthesia were performed for ESD of 94 lesions (82 patients) and 16 lesions (16 patients), respectively. The pathological findings showed that four patients had adenocarcinoma, and the lesions were most commonly identified in the L segment. The tumor size and resected specimen size showed no significant differences (Table 3).

Procedure outcomes and adverse events

The procedure time with non-general anesthesia was shorter than with general anesthesia (p=0.033). Although there were no significant differences in incidences of adverse events between the two groups, all adverse events were safely and successfully managed during the procedure. Although no perforation was found in both groups, mediastinal emphysema occurred in 12 cases (12.2%) under general anesthesia and 1 case (1.02%) under non-general anesthesia. In 12 cases with mediastinal emphysema in the general anesthesia group, eight cases did not show the presence of any muscle damage. There were no treatment-related deaths (Table 4).

Table 1. Baseline characteristics of the 170 superficial esophageal carcinoma in 151 patients underwent ESD or EMR

Characteristic	Total (n=151)	ESD (n=98)	EMR (n=53)	p
Patient characteristics				
Age, years				0.220
Mean±SD	67.5±9.7	68.3±9.8	66.0±9.4	
Median (range)	68 (43–89)	68 (43–89)	68 (45–86)	
Gender				0.611
Male	125 (82.8%)	80	45	
Female	26 (17.2%)	18	8	
Daily habits				
Smoking	124 (82.1%)	85	39	*0.044
Daily drinking	126 (83.4%)	87	39	*0.016
Comorbidities				
Esophageal hiatal hernia	59 (39.1%)	41	18	0.344
Barrett's esophagus	48 (31.8%)	33	15	0.499
LSBE	3 (2.0%)	3	0	
SSBE	45 (29.8%)	30	15	

ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; LSBE: long-segment Barrett's esophagus; SSBE: short-segment Barrett's esophagus
*significant

DISCUSSION

It was previously reported that esophageal ESD causes major adverse events such as perforation in the rate of 4.0%–6.0%. It is also well known that esophageal ESD not only causes major adverse events such as emphysema but is also very time-consuming, as stated in previous reports (20,21). This indicates that ESD has a disadvantage compared with EMR, which has been shown to be a safe and simple technique requiring a relatively short period of time (22,23). The factors associated with mediastinal emphysema have been reported as the exposure of the muscular layer and lesion located in the lower part of the esophagus (24), but these have not been considered regarding anesthetic methods during ESD (25). In addition, carbon dioxide (CO_2) has been recently used for insufflation during ESD (26). CO_2 is absorbed faster in the body than air, and it is rapidly excreted through respiration. The use of CO_2 insufflation in ESD procedures not only reduces patient discomfort but also reduces the risk of severe mediastinal emphysema and pneumothorax in cases of perforation.

To the best of our knowledge, this is the first report to examine the treatment outcomes of esophageal ESD with respect to anesthetic methods. Esophageal ESDs performed in our hospital have a significantly higher risk of adverse events (7.0% of me-

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Table 2. Baseline characteristics of the subject

Lesion characteristic	Total (n=170)	ESD (n=110)	EMR (n=60)	p
Lesion size, mm				*<0.001
Mean±SD	17.2±12.9	22.0±13.3	8.3±5.0	
Median (range)	12.5 (1–60)	20 (1–60)	7.5 (2–30)	
Location				0.655
U	52 (30.6%)	32	20	
M	93 (54.7%)	63	30	
L	25 (14.8%)	15	10	
Morphology				*<0.001
0-IIa	22 (12.9%)	16	6	
0-IIb	65 (38.2%)	27	38	
0-IIc	83 (48.8%)	67	16	
Histology				0.135
Squamous cell carcinoma	166 (97.6%)	106	60	
Adenocarcinoma (developed from SSBE)	4 (2.4%)	4	0	
Depth				0.123
M	150 (88.2%)	93	57	
SM	19 (11.2%)	16	3	
MP	1 (0.59%)	1	0	
Procedure characteristics				
Anesthesia method				0.059
General anesthesia	98 (57.6%)	94	4	
Non-general anesthesia	72 (42.4%)	16	56	

ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; LSBE: long-segment Barrett's esophagus; SSBE: short-segment Barrett's esophagus; M: mucosa; SM: submucosa; MP: muscularis propria
*significant

diastinal emphysema and pulmonary atelectasis) than EMR. In the present study, there were no significant differences for the incidence of adverse events such as mediastinal emphysema and pulmonary atelectasis between general and non-general anesthesia. This is because of the difference of operator levels. It is of course well-established that endoscopic manipulation in ESD under non-general anesthesia by experts is stabilized. On the other hand, physicians with various levels of experience performed esophageal ESD under general anesthesia. However, it is known that adverse events, particularly mediastinal emphysema by muscle damage or exposure of the muscular layer, did not cause a critical outcome. Because all endoscopic procedures performed in difficult conditions during ESD might be well maneuverable under general anesthesia. High intramediastinal pressure renders precise endoscopic maneuverability under a clear visual field difficult. Severe mediastinal emphysema may lead to shock. The mediastinal pressure is higher than the intra-esophageal pressure under closed-circuit anesthesia

Table 3. Univariate analysis for clinicopathological factors between general anesthesia and non-general anesthesia in cases of superficial esophageal carcinoma underwent ESD

Variable	General anesthesia	Non-general anesthesia	p
Number of patients	82	16	
Number of lesions	94	16	
Patient-related factors			
Median age (range) (years)	68 (43–88)	66.5 (50–89)	0.962
Gender (male/female)	65/17	15/1	
Comorbidities			
Esophageal hiatal hernia	34	7	0.865
Barrett's esophagus	27	6	0.723
Lesion related factors			
Mean size of tumor (range) (mm)	22.2 (1–60)	20.6 (3–40)	0.654
Mean size of specimen (range) (mm)	34.8 (3–88)	33.3 (16–50)	0.700
Location			*0.001
U	31	1	
M	55	8	
L	8	7	
Morphology			0.069
0-IIa	10	5	
0-IIb	22	4	
0-IIc	62	7	
Histology			*0.001
Squamous cell carcinoma	93	13	
Adenocarcinoma	1	3	
Depth			0.411
M	81	12	
SM	12	4	
MP	1	0	
Procedure reveled factor			
Operator level (experts/non-experts)	16/78	14/2	*<0.001

ESD: endoscopic submucosal dissection; LSBE: long-segment Barrett's esophagus; SSBE: short-segment Barrett's esophagus; M: mucosa; SM: submucosa; MP: muscularis propria
*significant

(general anesthesia), which prevents mediastinal emphysema. Consequently, general anesthesia is preferable for large esophageal lesions that require ≥2 h to complete esophageal ESD. Thus, in general, general anesthesia is considered a more safe method for esophageal ESD.

There are limitations to this study. This is a retrospective study in a single institution. Also, there were no preset criteria to assign patients to the general anesthesia or conscious sedation groups.

Table 4. Univariate analysis for procedure outcomes between general anesthesia and non-general anesthesia in cases superficial esophageal carcinoma underwent ESD

Variable	General anesthesia	Non-general anesthesia	p
Mean procedure time (range) (min)	102.3 (20–480)	75.4 (20–180)	*0.033
Adverse events	12	1	0.456
Perforation	0	0	–
Muscle damage	4	1	0.723
Delayed bleeding	0	0	–
Mediastinal emphysema	11	1	0.518
Pulmonary atelectasis	1	0	0.679

ESD: endoscopic submucosal dissection

However, we assume that general or non-general anesthesia has been reasonably selected based on clinical information that is carefully assessed using endoscopic images or patient status before endoscopic resection.

Even by non-experts, esophageal ESD was successfully achieved under general anesthesia because adverse events could be safely and successfully controlled. In conclusion, we would like to recommend that general anesthesia might be a crucial option in esophageal ESD.

Ethics Committee Approval: Ethics Committee Approval was not received due to the retrospective nature of the study.

Informed Consent: Written informed consent was obtained from patients who participated in this study

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.G.; Design - T.G.; Supervision - T.I., F.M.; Materials - N.Y.K.; Data Collection and/or Processing - N.Y.K.; Analysis and/or Interpretation - S.S., S.M.; Literature Review - T.G., S.S.; Writer - N.Y.K.; Critical Review - T.G., S.S., S.M., T.I., F.M.

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