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## Retrospective Study

# Endoscopic submucosal dissection for early esophageal neoplasms using the stag beetle knife

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## Abstract

### AIM

To determine short- and long-term outcomes of endoscopic submucosal dissection (ESD) using the stag beetle (SB) knife, a scissor-shaped device.

### METHODS

Seventy consecutive patients with 96 early esophageal neoplasms, who underwent ESD using a SB knife at

Kure Medical Center and Chugoku Cancer Center, Japan, between April 2010 and August 2016, were retrospectively evaluated. Clinicopathological characteristics of lesions and procedural adverse events were assessed. Therapeutic success was evaluated on the basis of *en bloc*, histologically complete, and curative or non-curative resection rates. Overall and tumor-specific survival, local or distant recurrence, and 3- and 5-year cumulative overall metachronous cancer rates were also assessed.

## RESULTS

Eligible patients had dysplasia/intraepithelial neoplasia (22%) or early cancers (squamous cell carcinoma, 78%). The median procedural time was 60 min and on average, the lesions measured 24 mm in diameter, yielding 33-mm tissue defects. The *en bloc* resection rate was 100%, with 95% and 81% of dissections deemed histologically complete and curative, respectively. All procedures were completed without accidental incisions/perforations or delayed bleeding. During follow-up (mean, 35 ± 23 mo), no local recurrences or metastases were observed. The 3- and 5-year survival rates were 83% and 70%, respectively, with corresponding rates of 85% and 75% for curative resections and 74% and 49% for non-curative resections. The 3- and 5-year cumulative rates of metachronous cancer in the patients with curative resections were 14% and 26%, respectively.

## CONCLUSION

ESD procedures using the SB knife are feasible, safe, and effective for treating early esophageal neoplasms, yielding favorable short- and long-term outcomes.

**Key words:** Neoplasms; Stag beetle knife; Esophageal; Endoscopic submucosal dissection; Outcome measures

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**Core tip:** Various devices designed for endoscopic submucosal dissection (ESD) are currently under investigation for their usefulness in the treatment of early esophageal neoplasms. This study aimed to evaluate the short- and long-term outcomes of ESD using the stag beetle (SB) knife, a scissor-shaped device. Seventy-four patients with 101 esophageal lesions underwent resection via SB-knife ESD. Rates of *en bloc*, histologically complete, and curative resections were 100%, 95%, and 81%, respectively. The 3- and 5-year survival rates were 83% and 70%, respectively. The SB knife allows safe and effective ESD of early esophageal neoplasms.

Kuwai T, Yamaguchi T, Imagawa H, Miura R, Sumida Y, Takasago T, Miyasako Y, Nishimura T, Iio S, Yamaguchi A, Kouno H, Kohno H, Ishaq S. Endoscopic submucosal dissection for early esophageal neoplasms using the stag beetle knife. World

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## INTRODUCTION

Esophageal carcinoma is the eighth most common cancer worldwide and the sixth leading cause of cancer-related deaths globally<sup>[1,2]</sup>. Squamous cell carcinoma (SCC) is the commonest histotype of esophageal cancer in Japan and worldwide<sup>[1,3]</sup>. Despite advances in diagnosis and treatment, outcomes in these patients remain poor, with five-year survival rates of 15%-20%<sup>[4,5]</sup>. Aggressive use of enhanced imaging for screening and advanced magnification endoscopy systems have aided in early diagnosis. However, given the many possible comorbidities in patients undergoing conventional treatments (such as esophagectomy) and the greater likelihood of incomplete resection through endoscopic mucosal resection, researchers are now actively investigating endoscopic submucosal dissection (ESD) of superficial esophageal neoplasms<sup>[6-8]</sup>.

A number of conventional ESD devices (*i.e.*, dual, flush, insulated-tip, and hook knives) have been utilized for esophageal ESD<sup>[9-14]</sup>. Compared to those of the stomach, the thin wall (with no serosa) and narrow lumen of the esophagus make ESD inherently more challenging. The endoscopic maneuverability difficulties imposed by conventional ESD devices are also problematic, particularly the lack of fixation to targets and the fact that these devices are partially or entirely uninsulated. Constraints of this sort are conducive to unintentional incisions, increasing the potential risk of adverse events such as perforation and mediastinal emphysema<sup>[15-18]</sup>.

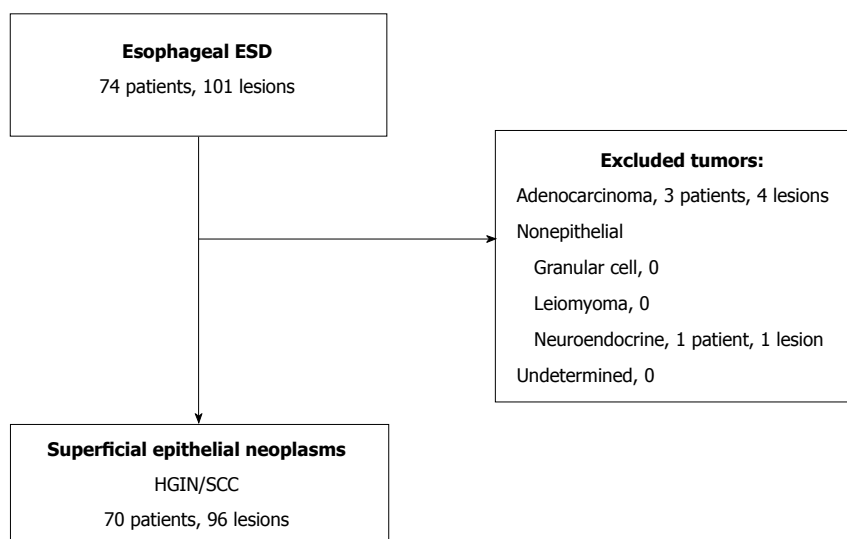
On the other hand, the stag beetle (SB) knife (Sumitomo Bakelite Co., Ltd., Akita, Japan), with its ability to grasp, assess, and then cut targeted tissue, allows endoscopists to maintain adequate dissection planes, preventing inadvertent injury to the muscular layer and promoting safe ESD<sup>[19-23]</sup>. Although early experiences at selected institutions suggest that the SB knife is safe and effective, no large series of patients or long-term outcomes have been reported to date<sup>[21-24]</sup>. The aim of this study was to investigate use of the SB knife for ESD of early esophageal neoplasms, assessing both feasibility and safety. Subsequent short- and long-term clinical outcomes were examined as well.

## MATERIALS AND METHODS

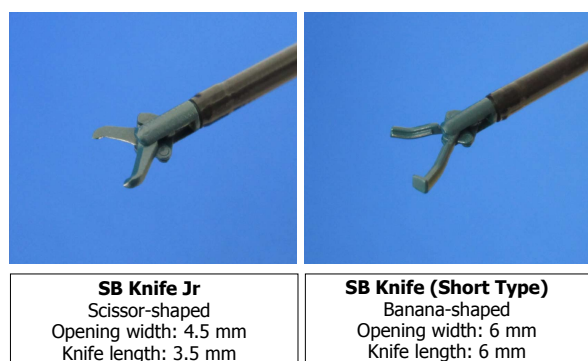
### Study design

A single-center retrospective review of collected data was conducted, examining 74 consecutive patients with 101 esophageal lesions who underwent resection via SB-knife ESD between April 2010 and August 2016 at Kure Medical Center and Chugoku Cancer Center,





**Figure 1 Study design, evaluating the use of the stag beetle knife for esophageal endoscopic submucosal dissection.** ESD: Endoscopic submucosal dissection; HGIN: High-grade intraepithelial neoplasia; SCC: Squamous cell carcinoma.



**Figure 2 Features of the stag beetle Knife Jr and short devices.**

Japan (Figure 1). All patients underwent resection using only SB-knife ESD during this time period. Approved by the National Hospital Organization Kure Medical Center and the Chugoku Cancer Center Institutional Review Board Ethics Committee on 3 October 2016, the study incorporated good clinical practice, conforming to Declaration of Helsinki principles. All lesions were diagnosed preoperatively during chromoendoscopy, identifying areas for biopsy through narrow-band imaging or iodine staining. Inclusion criteria were patients with superficial esophageal neoplasms (SENs), consisting of high-grade intraepithelial neoplasia or SCC. Exclusion criteria included patients with adenocarcinoma, non-epithelial tumors (*i.e.*, granular cell tumors, leiomyomas, and neuroendocrine tumors) or undetermined tumors.

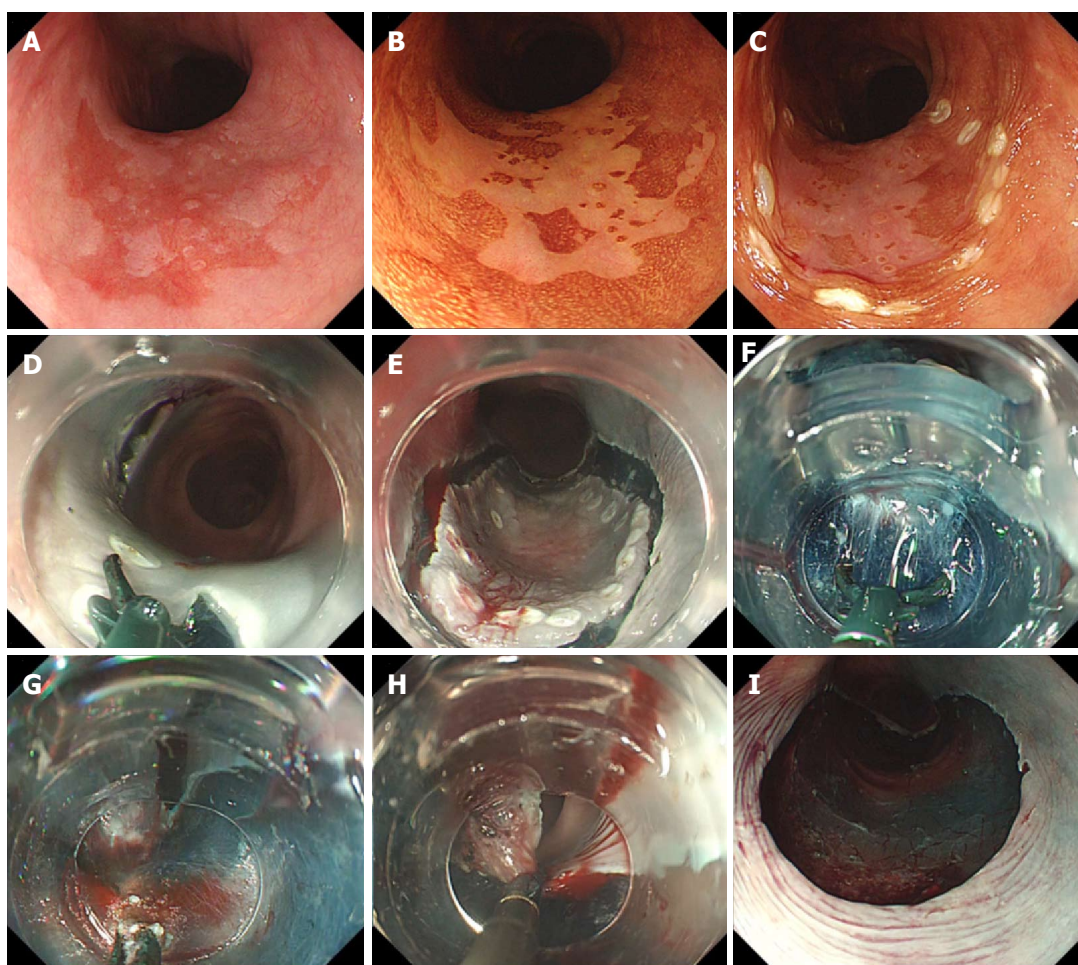
All patients were informed of the risks and benefits of ESD and provided written informed consent. ESD was contraindicated in patients with serious comorbidities, distant metastasis, or massive submucosal invasion.

### ESD procedure

ESD procedures were performed by four board-certified

endoscopists of the Japan Gastroenterological Endoscopy Society, three with no previous conventional esophageal ESD experience and one with low experience (10 cases). Patients received intravenous nitrazepam for sedation, and cardiorespiratory function was monitored throughout the procedure. A single-channel endoscope equipped with a water jet (GIF-H260Z; Olympus Corp, Tokyo, Japan) and attached transparent tip hood was routinely used, along with carbon dioxide insufflation. Initially, the outside margin of each lesion was marked using argon plasma coagulation in forced coagulation mode; the esophageal mucosa was injected with 0.4% sodium hyaluronate (MucoUp; Seikagaku Corp., Tokyo, Japan) mixed with a small amount of indigo carmine. Circumferential excision was then carried out with the SB Knife Jr (4.5-mm opening width, 3.5-mm length; Sumitomo Bakelite Co.) (Figure 2). For submucosal dissection, the SB Knife Short (6-mm opening width, 6-mm length) (Figure 2) was often preferred, because detachment/peeling of the submucosa was faster, and it was less likely to engage the muscular layer, given the curved shape of the blade. The SB knife allowed grasping of the targeted segment, which was then cut using a high-frequency generator (VIO300D; ERBE, Tübingen, Germany) in the endo-cut Q mode (effect 1) for incising mucosa and dissecting submucosa. The soft coagulation mode (effect 5.40 W) was used for hemostasis. If repeated coagulation was required, hemostatic forceps (Coagrasper; Olympus Corp.) were applied to facilitate endoscopic hemostasis. The procedure was continued until resection was completed (Figure 3).

In instances of semi-circumferential or circumferential ESD, intralesional diluted triamcinolone acetonide injected on postoperative day 2 [Kenacort (40–80 mg); Bristol-Myers Squibb Co., New York, NY, United States] or oral prednisolone (30 mg/d) was prescribed and tapered gradually over several weeks<sup>[25]</sup> to prevent



**Figure 3** Stag beetle knife used for esophageal endoscopic submucosal dissection in a 79-year-old man. Endoscopic appearance of a 35-mm, depressed lesion in the middle one-third of the esophagus (A) under white light (B) on a scatter image with Lugol's iodine applied (C) with argon plasma coagulation markings; D and E: Use of the SB Knife Jr for full-circumferential incision; use of the SB Knife Short for (F) submucosal dissection and (G) hemostasis; H: *En bloc* resection of the lesion; I: Ulcer floor after resection.

postoperative stricture<sup>[26,27]</sup>.

### Histopathology and short-term outcomes

Resected specimens were immediately fixed in 10% buffered formalin, with samples later selected for routine processing, embedding in paraffin, and slide preparation (3–4  $\mu$ m, hematoxylin & eosin stain). The histotype, depth of invasion, and resection margins (vertical and lateral) of the lesions were assessed microscopically (Figure 4) using an optical micrometer to measure invasive areas. The tumor size, anatomic location (upper one-third, middle one-third, or lower one-third of the esophagus), and extent (%) of esophageal circumferential involvement were documented. Rates of *en bloc* resection, histologically complete resection (*i.e.*, *en bloc* resection with negative lateral and vertical margins), and curative or non-curative resection served as indices of therapeutic success. Curative resection was defined as complete tumor resection with invasion  $\leq$  200  $\mu$ m below the deep border of the lamina muscularis mucosae and no lymphovascular involvement<sup>[8]</sup>.

### Adverse events

Immediate adverse events such as perforation, delayed bleeding, and postoperative pneumonia and delayed adverse events such as esophageal stricture were recorded.

### Long-term outcomes

To monitor patients, esophagogastroduodenoscopy was performed 3–6 mo and 1 year following ESD and annually thereafter; computed tomography was also performed annually. Three- and 5-year overall survival rates were assessed for the entire study cohort. SENS detected > 1 year after curative resection by ESD were considered metachronous cancers. Cumulative overall metachronous cancer rates during the 3- and 5-year periods were also assessed.

### Statistical analysis

Continuous variables were expressed as a mean  $\pm$  standard deviation or median and range, as appropriate, and categorical variables as frequency or number of

**Table 1 Study demographics and clinicopathologic characteristics *n* (%)**

Characteristics	Value
Number of patients	70
Number of lesions	96
Age, mean $\pm$ SD (range), yr	67 $\pm$ 10 (43-87)
Sex	
Male	59 (84)
Female	11 (16)
Location of the tumor in the esophagus	
Upper one-third	11 (11)
Middle one-third	53 (55)
Lower one-third	33 (34)
Gross appearance	
Depressed	86 (90)
Elevated	7 (7)
Flat	2 (2)
Mixed	1 (1)
Resected specimen size, mean $\pm$ SD (range), mm	33 $\pm$ 14 (9-75)
Resected tumor size, mean $\pm$ SD (range), mm	24 $\pm$ 13 (1-64)
Luminal extent	
< 1/2	59 (61)
$\geq$ 1/2, < 2/3	20 (21)
$\geq$ 2/3	17 (18)
Histopathologic features	
Dysplasia/intraepithelial neoplasia	21 (22)
Squamous cell carcinoma	75 (78)
Epithelial lining	15 (20)
Lamina propria mucosae	31 (41)
Muscularis mucosae	13 (17)
Submucosa (SM1)	2 (3)
Submucosa (SM2 or deeper)	14 (19)

**Table 2 Short-term outcomes and adverse events of esophageal endoscopic submucosal dissection, *n* %**

	95%CI
Procedure duration, median (range)	60 (25-305)
<i>En bloc</i> resection	96 (100) [96.2-100]
Complete resection with negative margins	91 (95) [88.4-97.8]
Curative resection	78 (81) [72.3-87.8]
Adverse events	
Perforation	0 (0) [0-3.9]
Delayed bleeding	0 (0) [0-3.9]
Pneumonia	3 (3) [1.1-8.8]
Esophageal stricture	7 (7) [3.6-14.3]

occurrences. Kaplan-Meier curves were generated to analyze survival and metachronous cancer rates. A log-rank test was used to evaluate the significance of differences between curves, and a *P* value of less than 5% was considered significant. All statistical analyses were performed using JMP software (SAS Institute, Inc., Cary, NC, United States).

## RESULTS

### Demographic and clinicopathologic characteristics

A total of 96 SENs in 70 patients qualified for analysis. One subject was excluded, having received a final diagnosis of nonepithelial tumor, and 4 subjects were excluded, having received a final diagnosis of adenocar-

cinoma (Figure 1). Fifteen patients had multiple lesions, harboring two (*n* = 9), three (*n* = 3), four (*n* = 1), or five (*n* = 2) lesions. Mean age of the study population (*n* = 70; 84% men) was 67  $\pm$  10 years (Table 1). By location, 11% of lesions involved the upper one-third of the esophagus, 55% the middle one-third, and 34% the lower one-third. Macroscopically, majority of the lesions were depressed (90%) rather than elevated (7%) or flat (2%).

Resected specimens measured 33  $\pm$  14 mm on average, with a mean tumor size of 24  $\pm$  13 mm. Most tumors (61%) involved < one-half of the esophageal luminal circumference. Histopathological diagnoses were as follows: dysplasia/intraepithelial neoplasia (22%), or SCC (78%). Typically, invasive SCCs were limited to the lamina propria mucosae (41%), with SM2 or deeper infiltration accounting for 19% (Table 1).

### Short-term outcomes

Short-term outcomes are summarized in Table 2. The median procedural time was 60 min (range, 25-305 min). Rates of *en bloc* resection, histologically complete resection, and curative resection were 100%, 95%, and 81%, respectively.

### Adverse events

All lesions were safely resected without any unintentional incisions/perforations or delayed bleeding episodes. Pneumonia was observed in 3% of patients and managed through antibiotic treatment. To prevent postoperative stricture after semi-circumferential ESD, intralesional injection of triamcinolone acetonide (3 patients) or oral prednisolone (7 patients) was administered. Esophageal strictures were encountered in seven patients, one requiring balloon dilatation (Table 2).

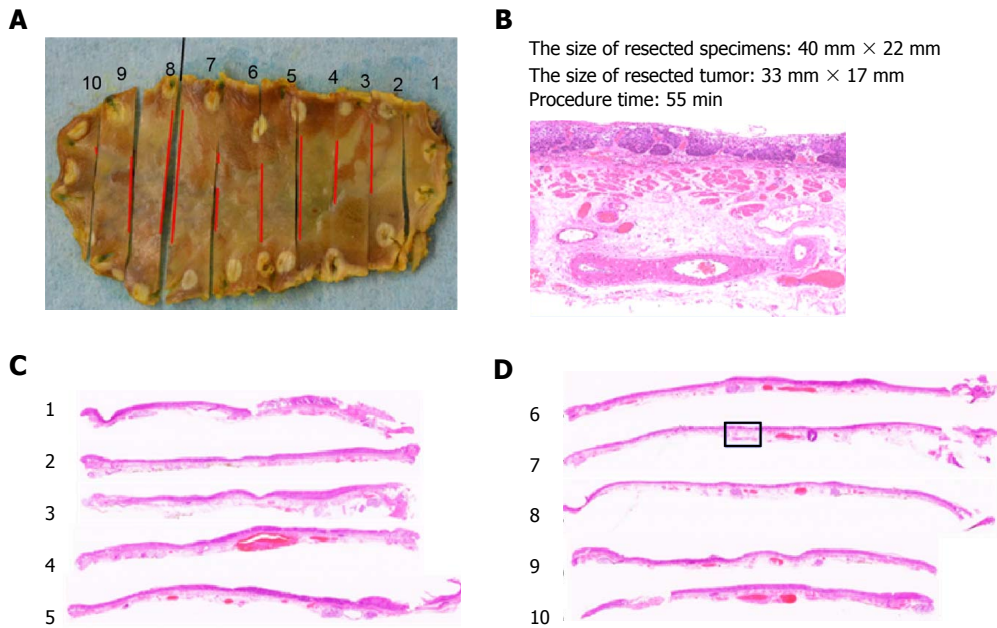
### Long-term outcomes

Curative resection was achieved in 57 patients, three of whom received additional chemoradiotherapy (CRT). One of these three patients later developed metachronous cancer. Seven of the 54 patients who were given no additional treatment also developed metachronous cancers. The 3- and 5-year cumulative rates of metachronous cancer in patients with curative resections were 14% and 26%, respectively (Figure 5A). Non-curative resection was achieved in 13 patients, seven of whom underwent additional treatment, either surgery (*n* = 4), chemotherapy (*n* = 1), or CRT (*n* = 2). No instances of local recurrence or metastasis were observed in any patient during the mean follow-up period of 35  $\pm$  23 mo.

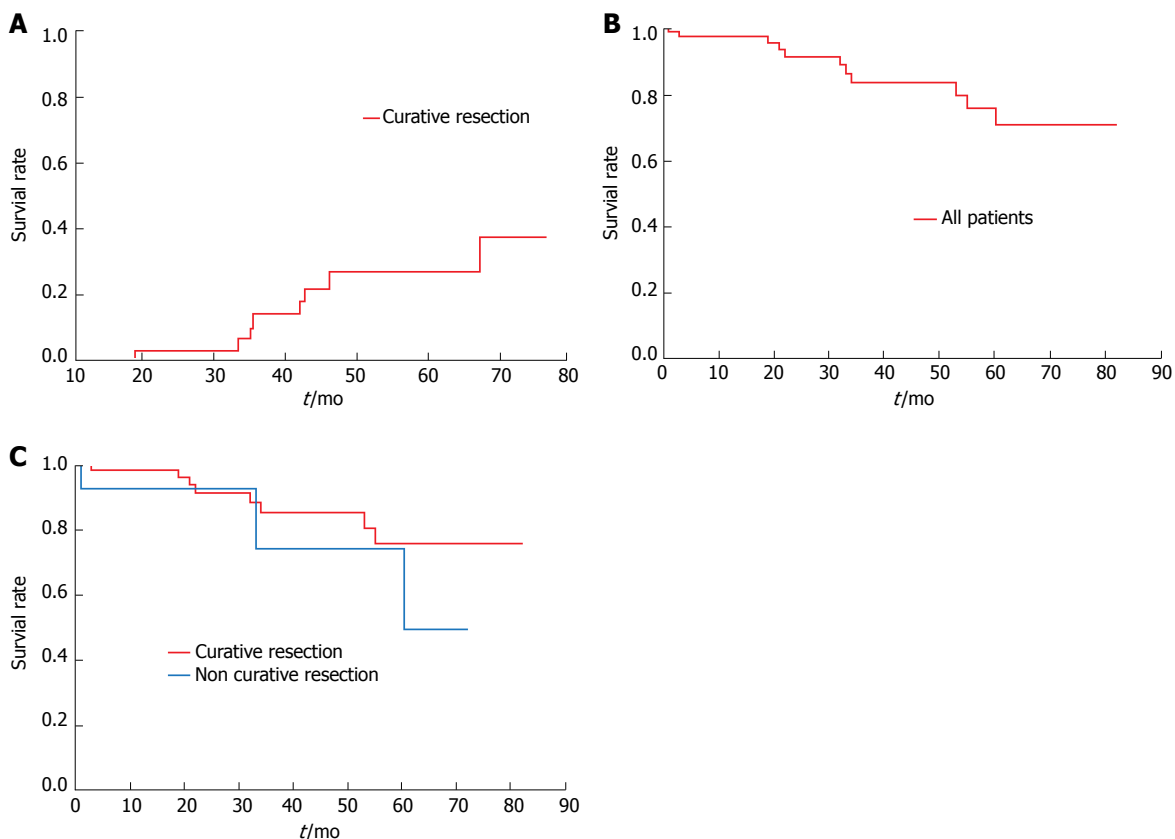
### Survival analysis

Three- and 5-year overall survival rates for the study cohort were 83% and 70%, respectively (Figure 5B), with corresponding rates of 85% and 75% in curative resections, and 74% and 49% in non-curative resections (Figure 5C). However, the difference in survival between curative and non-curative resections





**Figure 4** Formalin-fixed specimen sliced at 2-mm intervals for routine processing and slide preparation (A); Evaluation of the histotype, invasion depth, and vertical/lateral resection margins (B-D).



**Figure 5** Long-term outcomes and survival analysis. A: Cumulative metachronous cancer rates in patients with curative resection; B: Kaplan-Meier analysis of overall survival rates in all patients; C: Patients grouped according to curative and non-curative resection.

by ESD was not statistically significant. Eleven of 70 patients (curative resections, 8/57; non-curative resections, 3/13) died during follow-up. In patients with curative resections, causes of death included isolated instances of unknown primary cancer, hepatocellular

carcinoma, lung cancer, pharyngeal carcinoma, drowning, and aspiration pneumonia, as well as two instances of interstitial pneumonia. Causes of death after non-curative resection were oropharyngeal carcinoma, liver cirrhosis, and aspiration pneumonia,

each a single occurrence. None of the deaths was directly attributable to esophageal neoplasms.

## DISCUSSION

Our study suggests that the SB knife is safe and effective when used for ESD of early esophageal neoplasms. This technique resulted in high rates of *en bloc* resection (100%), histologically complete resection (95%), and curative resection (81%), with a low incidence of procedural adverse events, despite three of the certified endoscopists having either limited or no experience of esophageal ESD. Specifically, there were no unintentional incisions/perforations or delayed bleeding events. Furthermore, no patient experienced local recurrences or metastases in the long term, and the overall survival rates were highly favorable and similar to those for other devices<sup>[8,28,29]</sup>.

Data reported here are consistent with those of a previous study demonstrating the safety and efficacy of the SB knife as a means of esophageal ESD in 15 patients<sup>[23]</sup>. Importantly, overall adverse events for the SB knife are relatively low<sup>[10-14]</sup>. Its unique scissor-action allows surgeons to grasp and pull the targeted tissue away from the muscularis and then inspect the area before cutting for more controlled resection and avoidance of perforation. Unlike other devices<sup>[30,31]</sup>, no complex adjustments or special endoscopic techniques are required. This facilitated the acquisition of implementation skills by even general endoscopists<sup>[19,30]</sup> and shortened the training process<sup>[31-34]</sup>, and we obtained good results from the first case itself. The notable absence of perforation reflects the safe and easy use of the SB knife in this setting, despite cyclic respiratory and cardiac fluctuations encountered during esophageal ESD. This tool also acts as a hemostatic clamp, eliminating the need for separate hemostatic forceps, making the procedure simple and cost-effective, and encouraging high resectability rates.

We would like to emphasize that no tumors recurred when the SB knife was used for esophageal ESD. Earlier studies have already reported positive short-term treatment outcomes (*i.e.*, resection rates) using the SB knife in small series<sup>[23,24]</sup>. The present results indicate for the first time, in the largest series reported to date, that use of the SB knife offers excellent short- and long-term outcomes in treating early esophageal neoplasms. The high resection rates achieved and absence of local recurrence or metastasis during  $35 \pm 23$  mo of follow-up constitute a new paradigm shift in the treatment of SEN<sup>[14,16,17,28,35]</sup>. Consistent with other published studies<sup>[36]</sup>, several of our patients with curative resections (8/57) developed metachronous lesions, including one of three who received additional CRT. This finding underscores the need for follow-up monitoring on a regular basis.

On analyzing longer-term patient outcomes, 3- and 5-year survival rates tended to be slightly, but not significantly, poorer if resections were non-curative

(74% and 49%, respectively) rather than curative (85% and 75%, respectively). Although non-curatively resected esophageal cancer is typically associated with a poor prognosis, none of the deaths recorded in the present study were a direct result of esophageal cancer. The aforementioned trend may then have a singular explanation. As ESD ordinarily is not indicated in patients with SM-level invasive cancer, such patients who agreed to undergo ESD for excisional biopsy (the goal being localized control) were included in the non-curative resection group. Consequently, it appears that achieving local control of esophageal cancer *via* ESD is quite feasible in elderly patients and in those with serious underlying diseases, who ultimately may die from other causes. By seemingly benefitting from the safe performance of esophageal ESD, we have thereby demonstrated the efficacy of the SB knife in a high-risk population.

Contrary to earlier concerns that the use of the SB knife might prolong ESD procedures<sup>[16,18]</sup>, we found that it greatly expedited ESD. The median time needed to complete ESD was 60 min (mean, 78 min), approximating the time required for conventionally performed ESD (median, 90 min) in one large multicenter study<sup>[8]</sup>.

Our study has three limitations. It is retrospective, although data were collected from consecutive patients, it was conducted at a single center; and no comparison with another device was attempted. However, strengths of the study include the sizeable patient population and the extended follow-up period, both providing valuable data on the feasibility, safety, and efficacy of SB knife usage for esophageal ESD.

In conclusion, ESD procedures using the SB knife are feasible, safe, and effective for treating early esophageal neoplasms, yielding favorable short- and long-term outcomes. No perforation occurred in our study population, attesting to the innovative design of the SB knife, which allows better control for safer dissection. The availability of this tool may promote widespread adoption of ESD to treat early-stage cancers of the esophagus. There is need to conduct RCT studies to compare this new innovative device with established devices.

## ARTICLE HIGHLIGHTS

### Research background

Several conventional endoscopic submucosal dissection (ESD) devices have been utilized for esophageal ESD. The thin wall with no serosa and narrow lumen of the esophageal wall make ESD more challenging in the esophagus. The restricted endoscopic maneuvering required with conventional ESD devices is also problematic owing to lack of fixation to targets and the fact that these devices are partially or entirely uninsulated. These factors can lead to unintentional incisions, increasing the potential risk of adverse events such as perforation and mediastinal emphysema.

### Research motivation

The stag beetle (SB) knife, with its ability to grasp, assess, and then cut the targeted tissue allows endoscopists to maintain adequate dissection planes, preventing inadvertent injury to the muscular layer for safe ESD. Because of these advantages, the SB Knife is gaining acceptance, but relevant long-term

outcome data is limited.

## Research objectives

The aim of this study was to investigate use of the SB knife for ESD of early esophageal neoplasms, assessing both feasibility and safety. The subsequent short- and long-term clinical outcomes were examined as well.

## Research methods

We retrospectively reviewed 70 consecutive patients with 96 early esophageal neoplasms (HGIN/SCC) treated using ESD. An SB knife was used routinely in all procedures. Clinicopathologic characteristics of the lesions and rates of procedural adverse events, *en bloc* and histologically complete resection, overall and tumor-specific survival, and local or distant recurrence were assessed.

## Research results

The *en bloc* resection rate was 100%, with 95% and 81% of dissections deemed histologically complete and curative, respectively. All procedures were completed without accidental incisions/perforations or delayed bleeding. During follow-up (mean, 35 ± 23 mo), no local recurrences or metastases were observed. The 3- and 5-year survival rates were 83% and 70%, respectively. The 3- and 5-year cumulative rates of metachronous cancer in the patients with curative resections were 14% and 26%, respectively.

## Research conclusions

ESD procedures using the SB knife are feasible, safe, and effective for treating early esophageal neoplasms, yielding favorable short- and long-term outcomes. No perforation occurred in our study population, attesting to the innovative design of the SB knife, which allows better control for safer dissection.

## Research perspectives

The availability of this tool may promote widespread adoption of ESD to treat early-stage cancers of the esophagus. There is a need to conduct RCT studies to compare this new innovative device with established devices.

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