Introduction

Superficial duodenal epithelial neoplasia (SDET) was previously considered a rare disease [1–4]; estimated prevalence rates of 0.02% to 0.5% have been reported in autopsy series [5–7]. However, the ability to detect SDET has been increasing with recent advances in endoscopic technologies [8]. Due to the rarity of SDET, there are no established guidelines for treatment of SDET except for ampullary tumors [9].

Endoscopic mucosal resection (EMR) is a simple procedure but sometimes fails in piecemeal resection and is related to 20% to 30% of local recurrence after piecemeal EMR [10–12]. Alternatively, ESD achieves secure en bloc resection even in larger lesions [13–17]. Recently we reported that ESD achieved more than 90% of en bloc resection even in lesions larger than 20 mm [17]. On the other hand, previous studies reported that duodenal ESD is associated with more complications such as perforation and bleeding [17–25]. In particular, 13% to 50% incidence of perforation is reported in previous studies [17, 19, 20, 22–25]. Duodenal ESD is more effective as a secure local treatment but considered technically challenging.

If we can predict technical difficulty of ESD, it would have clinical impact in that we could better prepare according to technical difficulty for each patient. For example, we could choose general anesthesia in the operating room for cases in which technical difficulty is expected or conscious sedation in the endoscopy unit for cases anticipated to be easier. In other organs, such as the stomach and colorectum, some clinical fea-
tues of the lesion such as location and size would predict technical difficulty [26, 27]. However, to date, few studies have objectively analyzed predictors of technical difficulty of duodenal ESD. Therefore, the aim of the current study was to elucidate predictors of technical difficulty of duodenal ESD.

Patients and methods
Study design and patient eligibility
This was a retrospective observational study. From June 2010 to June 2017, a total of 174 consecutive patients with SDET who underwent resection with ESD at our institute were included. There was a case of intraoperative perforation requiring conversion to surgery, and that case was excluded from data analysis. This study was performed in accordance with the 2008 revision of the Helsinki Declaration. This is an accompanying research study [17], and patient consent was obtained in the original research study. The study protocol was approved by the institutional review board (20150221).

ESD procedure
In our institute, duodenal ESD is performed under either conscious sedation consisting of benzodiazepine, pethidine, and dexmedetomidine or general anesthesia with intratracheal intubation. The latter is applied for challenging cases (for example, lesions exceeding 40 mm or with poor scope maneuverability). ESD procedures were performed by six expert endoscopists who had performed more than 1,000 ESD procedures and at least 200 in each organ (esophagus, stomach, and colorectum) at the beginning of this study. ESD procedures were performed principally using a therapeutic endoscope with a water jet function (GIF-Q260J, Olympus Medical Systems, Tokyo, Japan). This endoscope has a 9.8-mm outer diameter, 3.2-mm working channel, and 210° upward angle.

A tapered tip hood was put on the tip of the endoscope to facilitate to enter narrow submucosal space (ST Hood Fujifilm Corp, Tokyo, Japan). Generally, a submucosal injection of 10% glycerine solution (Glyceol Chugai Pharmaceutical Co., Ltd, Tokyo, Japan) with epinephrine (dilution 1:400,000) was administered. In difficult cases, 0.4% sodium hyaluronate (Mucoup, Tokyo, Japan) was used as needed. A mucosal incision was made or submucosal dissection was performed using a DualKnife or a DualKnife J with a length of 1.5 mm (Olympus Medical Systems, Tokyo, Japan). A Hookknife (Olympus Medical Systems, Tokyo, Japan) was used in difficult cases, such as in cases with poor scope maneuverability. Minor bleeding was treated with these devices by placing the tip of the device into the outer sheath; however, in cases of spurring bleeding, hemostatic forceps (Coagrasper, Olympus Medical Systems, Tokyo, Japan) were used. These energy devices were powered by a high-frequency electrosurgical unit (VIO 300D, ERBE Elektromedizin, Tübingen, Germany) with dry cut (effect 3–30 W) for mucosal incision, swift coagulation (effect 4–30 W) for submucosal dissection, and soft coagulation (effect 5–50 W) for hemostasis.
the duodenum) were selected as influencing factors. Statistical analysis was performed using JMP software (ver. 13.0.0, SAS Institute, Inc., Cary, North Carolina, United States), and a *P* < 0.05 was considered statistically significant.

**Results**

**Patient characteristics**

Characteristics of patients included in the study are described in ►Table 1. Approximately 20% of lesions were located in the duodenal flexure. Mean lesion size was 27.4 ± 0.96 mm. More than 90% of lesions occupied a circumference of less than one-half the duodenum. There were three cases of local residual recurrence after previous treatment.

**Clinical outcomes of duodenal ESD**

Clinical outcomes of duodenal ESD are shown in ►Table 2. Resection in a single piece and R0 resection rate were performed in 97.7% and 84.4% of cases, respectively. In one case, conversion to laparoscopic partial duodenectomy was required due to massive bleeding and perforation caused by poor maneuverability of endoscope. Median procedure time was 50 minutes and 26.6% of patients had a procedure time longer than 100 minutes, which was the first quartile of the procedure time. Intraprocedural perforation occurred in 12.7% of the included patients. Thus, 34.5% of patients had technical difficulties during duodenal ESD.

**Predictors for difficult ESD, intraprocedural perforation, and prolonged procedure time**

We performed logistic regression analysis to determine predictors for difficult ESD, intraprocedural perforation, and prolonged procedure time. In univariate analysis, lesion location in the duodenal flexure, larger lesion size, and an occupied circumference of more than half the duodenum were associated with a significant increase in technical difficulty of duodenal ESD, while lesion location in the posterior wall was associated with significant decrease in technical difficulty of ESD. In multivariate analysis, lesion location in the duodenal flexure (OR, 2.61; 95% CI, 1.02 – 6.68), larger lesion size (OR, 5.26; 95% CI, 2.15 – 12.9), and an occupied circumference of more than half the duodenum (OR, 5.80; 95% CI, 1.83 – 18.4) were associated with a significant increase in technical difficulty (►Table 3).

Larger lesion size and an occupied circumference of more than half the duodenum were significantly associated with intraprocedural perforation in univariate analysis, while only larger lesion size was significantly associated with intraprocedural perforation (OR, 3.84; 95% CI, 1.22 – 12.1) in multivariate analysis (►Table 4).

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**Table 2** Clinical outcomes of duodenal ESD.

| Variable                   | Univariate | Multivariate |
|----------------------------|------------|--------------|
|                            |            |              |
| Procedure time             | Median [range], min | 50 [10 – 360] |
| > 100 min, n (%)           | 46 (26.6%) |
| Resection in a single piece| Present, n (%) | 170 (97.7%)  |
| R0 resection               | Present, n (%) | 147 (84.4%) |
| Perforation                | Present, n (%) | 22 (12.7%)   |
| Bleeding                   | Present, n (%) | 164 (5.2%)   |
| Cases with technical difficulty | Present, n (%) | 60 (34.5%)   |

**Table 3** Predictors of technical difficulty.

| Variable                  | Univariate | Multivariate |
|---------------------------|------------|--------------|
|                            | Odds ratio | 95% CI       | *P* value | Odds ratio | 95% CI       | *P* value |
| Location                  |            |              |          |            |              |          |
| Duodenal flexure (SDA/IDA)| 2.83       | 1.25 – 6.37  | 0.012<sup>1</sup> | 2.61       | 1.02 – 6.68  | 0.047<sup>1</sup> |
| Others                    | 1          | 1            |          | 1          | 1            |          |
| Site                      |            |              |          |            |              |          |
| Posterior wall            | 1.49       | 0.75 – 2.96  | 0.26     | 0.94       | 0.42 – 2.11  | 0.89     |
| Others                    | 1          | 1            |          | 1          | 1            |          |
| Lesion size               |            |              |          |            |              |          |
| > 40 mm                   | 1.08       | 0.86 – 1.53  | <0.01<sup>1</sup> | 5.26       | 2.15 – 12.9  | <0.01<sup>1</sup> |
| ≤ 39 mm                   | 1          | 1            |          | 1          | 1            |          |
| Occupied                  |            |              |          |            |              |          |
| More than 1/2             | 12.6       | 4.47 – 35.7  | <0.01<sup>1</sup> | 5.80       | 1.83 – 18.4  | <0.01<sup>1</sup> |
| Less than 1/2             | 1          | 1            |          | 1          | 1            |          |

SDA, supraduodenal angle; IDA, inferior duodenal angle.
<sup>1</sup> Statistically significant
Lesion location in the duodenal flexure, larger lesion size, and occupied circumference of more than half the duodenum were associated with a significant increase in technical difficulty of ESD in terms of prolonged procedure time, while lesion location in the posterior wall was associated with a significant decrease in technical difficulty of ESD in univariate analysis. In multivariate analysis, lesion location in the duodenal flexural (OR, 3.31; 95 % CI, 1.21–9.07), larger lesion size (OR, 5.59; 95 % CI, 2.20–14.2), and an occupied circumference of more than half the duodenum (OR, 7.83; 95 % CI, 2.52–24.3) were associated with a significant increase in technical difficulty (▶ Table5).

### Discussion

In this retrospective study, we tried to find predictors of technical difficulty of duodenal ESD through analysis of outcomes of duodenal ESD in 174 consecutive patients. Longitudinal lesion location in the duodenal flexure, lesion size larger than 40 mm, and an occupied circumference of more than half the duodenum were significantly associated with technical difficulty. In terms of intraprocedural perforation, larger lesion size was the only predictor, and for prolonged procedure time, longitudinal lesion location in the duodenal flexure, lesion size larger than 40 mm, and an occupied circumference of more than half the duodenum were independent predictors.

Advances in endoscopic devices and accumulation of knowledge of management of complications and technical tips for ESD have contributed to widespread of ESD especially in Japan. Many studies have revealed favorable outcomes of ESD with low morbidity rates, favorable R0 resection rates, and high organ preservation rates for lesions in the esophagus, stomach, and colorectum [14, 15, 28]. Thus, ESD for superficial esophageal, gastric, or colorectal epithelial lesions is a standard treatment in Japan. Indeed, more than 50 % of early gastric cancers are

| Variable | Univariate | Multivariate |
|----------|------------|--------------|
| Location | Duodenal flexure (SDA/IDA) | 1.56 | 0.52–4.62 | 0.44 |
|          | Others     | 1            | 1           |
| Site     | Posterior wall | 1.58 | 0.63–3.96 | 0.33 |
|          | Others     | 1            | 1           |
| Size of lesion | >40 mm | 5.04 | 1.99–12.8 | <0.01^ |
|          | ≤39 mm     | 1            | 1           |
| Occupied circumference | More than 1/2 | 5.12 | 1.92–13.7 | <0.01^ |
|          | Less than 1/2 | 1            | 1           |

SDA, supraduodenal angle; IDA, duodenal angle.
^1 Statistically significant

| Variable | Univariate | Multivariate |
|----------|------------|--------------|
| Location | Flexural part (SDA/IDA) | 3.27 | 1.43–7.47 | <0.01^ |
|          | Others     | 1            | 1           |
| Site     | Posterior wall | 0.43 | 0.19–0.97 | 0.032^ |
|          | Others     | 1            | 1           |
| Lesion size | >40 mm | 11.5 | 5.11–25.7 | <0.01^ |
|          | ≤39 mm     | 1            | 1           |
| Occupied circumference | More than 1/2 | 16.9 | 6.20–46.2 | <0.01^ |
|          | Less than 1/2 | 1            | 1           |

SDA, supraduodenal angle; IDA, inferior duodenal angle.
^1 Statistically significant
treated by ESD, and esophageal, gastric, and colorectal ESD have been approved by healthcare insurance.

On the other hand, duodenal ESD has been considered to be very high risk, with a 13% to 50% incidence of perforation in previous studies [19,20,22–25]. This high complication rate reflects the technical difficulty of duodenal ESD. In fact, the duodenum, especially the distal part, is very far from the mouth so that the maneuverability of the endoscope is often limited, and sometimes it is quite difficult to even approach the lesion. Due to the narrow space of the submucosal layer, it is difficult to go beneath the lesion. Burner’s glands and vessels are rich in the submucosal layer; therefore, visualization tends to be poor while dissecting this layer. Most importantly, the wall of the duodenum is extremely thin; therefore, perforation occurs easily [29].

As mentioned above, duodenal ESD is technically difficult; however, recent advances in devices and endoscopic techniques have contributed to improvement in outcomes. Recently, we reported a novel ESD technique, the “water pressure method,” which utilizes a pressure jet of water through a transparent hood with a small-caliber tip to open a narrow space in the submucosa after initial mucosal incision and submucosal dissection [30]. The pocket creation method (PCM) is also a novel endoscopic technique proposed by Miura and Yamamoto. In this method, a submucosal pocket is created at the beginning without extending the mucosal incision; as a result, stable conditions and good submucosal visualization can be obtained [31]. And a traction-assisted ESD technique has been reported [32,33]. Using these modified endoscopic treatments, outcomes of duodenal ESD have improved. In fact, in the latest report about short-term outcomes of duodenal ESD [17], the perforation rate was 15.5%, and this is one of the lowest incidences despite the large sample size of the study.

With improvement in outcomes, duodenal ESD is expected to become used more widely; therefore, it is important to identify features of difficult lesions. Here, we found that longitudinal lesion location in the duodenal flexure, lesion size larger than 40 mm, and occupied circumference of more than half the duodenum were significantly associated with technical difficulty of duodenal ESD. These findings would be helpful for risk stratification and management of patients undergoing duodenal ESD.

### Conclusion

In conclusion, the current study revealed that longitudinal lesion location in the duodenal flexure, lesion size larger than 40 mm, and occupied circumference of more than half the duodenum were significantly associated with technical difficulty of duodenal ESD. These findings would be helpful for risk stratification and management of patients undergoing duodenal ESD.

### Competing interests

None

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