Introduction
Duodenal neuroendocrine tumors (DNETs) are considered rare [1,2], occurring less frequently than rectal and gastric neu- roendocrine tumors (NETs) and accounting for <5 % of all gas- trointestinal NETs [1]. Endoscopic resection of DNETs remains controversial and its indications unclear. Endoscopic mucosal resection (EMR) [3,4], cap-assisted endoscopic mucosal resec-
tion (EMR-C) [3], endoscopic submucosal resection with liga-
tion (ESMR-L) [5–7], and endoscopic submucosal dissection
(ESD) [4,8,9] are deemed suitable for the resection of small
dNETs (≤10 mm) with a low malignancy potential. DNETs de-
velop from the deep mucosa and are histologically classified as
epithelial tumors and macroscopically as submucosal tumors
[10]. Thus, deep layer resection is required to achieve R0 resec-
tion. However, endoscopic treatment of DNETs has frequently

Endoscopic resection using an over-the-scope clip for duodenal
neuroendocrine tumors

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ABSTRACT

Background and study aims Endoscopic resection of duodenal neuroendocrine tumors (DNETs) remains contro-
versial, and its indications are still unclear. This study aimed to evaluate short-term outcomes of a newly developed
endoscopic muscularis resection (EMR) method that utilizes an over-the-scope clip (OTSC), termed EMRO, for treat-
ing DNETs.

Patients and methods In total, 13 consecutive patients with 14 small (≤10 mm) DNETs who underwent EMRO from
September 2017 to March 2020 were retrospectively enrol-
ed. EMRO was performed by a single experienced endos-
copist. Patients’ characteristics and treatment outcomes were assessed.

Results The En bloc and R0 resection rates were 100 % (14/14) and 92.9 % (13/14), respectively. The median patho-
logical resected specimen size was 10 mm, with a median
pathological resected tumor size of 6 mm. During the
EMRO procedure, there was no occurrence of misplacement
of the OTSC to the target lesion. With respect to the patho-
logical resection depth, nine cases (64.3 %) and five cases
(35.7 %) were categorized as deep submucosal resection
and muscularis resection, respectively, whereas no case
was categorized as full-thickness resection. There were no
intraoperative or delayed perforations. However, delayed
bleeding occurred in two cases. At a median follow-up of
12 months (range 7–36) after EMRO, there was no inci-
dence of local recurrence. At the first follow-up endoscopy
performed at 6 months after EMRO, the OTSC was retained
in place in two of 14 DNETs (14.3 %).

Conclusions EMRO can be performed safely, by an experi-
enced endoscopist, for small (≤10 mm) DNETs.

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resulted in incomplete resection [4], and endoscopists have to consider an increased risk of perforation when attempting to achieve an ample vertical safety margin in the thin duodenal wall. Therefore, an easy, safe, and reliable endoscopic resection procedure is needed for such lesions.

Recently, the over-the-scope clip (OTSC) system (Ovesco Endoscopy GmbH, Tübingen, Germany), a novel gastrointestinal full-thickness closure device, was reported to be safe and effective for fistula closure, anastomotic dehiscence, hemostasis of gastrointestinal bleeding, and endoscopic closure of iatrogenic gastrointestinal perforations [11]. Mucosal defect closure using the OTSC system after duodenal ESD has helped prevent the previously mentioned severe adverse events (AEs) [12,13]. Hence, we developed a new endoscopic resection method using the strong cerclage force of the OTSC, with the device placed prior to resection so as to surround the basal portion of the target lesion to achieve tumor resection deeper than the muscle layer and prevent intraoperative and delayed perforation. We termed this procedure endoscopic muscularis resection with OTSC (EMRO). In this study, our aim was to evaluate the short-term outcomes of EMRO for treating DNETs.

Patients and methods
Study design
This retrospective observational study was conducted at Saitama Medical University International Medical Center and performed in accordance with the Declaration of Helsinki. The study protocol was approved by our institution’s ethics committee (institutional ID: 19-315) and written informed consent was obtained from all patients after the risks and benefits of the treatment had been fully explained prior to EMRO.

Patients and methods
From September 2017 to March 2020, 13 consecutive patients with 14 DNETs ≤ 10 mm who underwent EMRO at our institute were enrolled. The inclusion criteria were: 1. Tumors diagnosed as NETs through preoperative pathological biopsy; 2. Lesions ≤ 10 mm in diameter identified on endoscopy; 3. Lesions located within the submucosal layer; and 4. No lymph node or distant metastasis detected. Considering the risk of acute pancreatitis, we did not attempt EMRO for lesions in which OTSC deployment could involve the major papillae. We excluded patients who refused the use of their resected tissue samples and clinical data for this study. All 14 EMRO procedures were performed by a single endoscopist (T.T.), who had performed > 250 duodenal endoscopic resections and > 200 OTSC procedures. Information on patient and clinical characteristics, including sex, age, tumor characteristics (location, size), short-term treatment outcomes, and follow-up outcomes (local recurrence and OTSC retention), was retrospectively assessed.

Preoperative endoscopic examination including simulation of OTSC deployment
Before considering EMRO, all patients underwent preoperative endoscopy using a therapeutic endoscope (GIF-Q260J or GIF-H290T; Olympus, Medical Systems Co., Tokyo, Japan). The lesion size, location, and position relative to the major papilla, and scope maneuverability were evaluated. Moreover, all patients underwent endoscopic ultrasonography to evaluate the depth of invasion (▶Fig. 1) and computed tomography (CT) to determine the presence of lymph node and/or distant metastasis.

The most critical step in the EMRO procedure is to avoid OTSC misplacement on the target lesion. OTSC misplacement was defined as deployment of the OTSC just onto the target lesion during the EMRO procedure. To avoid misplacement, we performed simulation of OTSC deployment during the preoperative endoscopic examination for all tumors deemed to be potential candidates for EMRO. The simulation was conducted as follows. First, an attachment cap (D-201-11804; Olympus) was mounted onto the tip of the endoscope so that the total length of the endoscope with the attachment cap was roughly similar to that of the endoscope with the applicator cap when the OTSC was mounted onto the endoscope tip. Second, we confirmed that the entire target tumor could be suctioned in-
side the attachment cap. We estimated the possibility and difficulty of en bloc resection of the lesion using EMRO (▶ Fig.2).

All patients had been referred from other hospitals, with preoperative biopsy completed prior to referral to our institution, with the histology of preoperative biopsies reviewed only by pathologists at the referring hospital. Histopathological assessments of resected specimens were performed by two experienced pathologists, according to the classification system of the World Health Organization [14]. In addition, immunohistochemical analysis, using chromogranin A and synaptophysin as neuroendocrine markers, was performed for accurate diagnosis; classification of tumors as G1, G2, or G3 was determined using the Ki-67 index.

**EMRO procedure**

All procedures were performed in an endoscopy room, with the patient under conscious sedation. EMRO procedures were performed using the same therapeutic endoscope as in preoperative endoscopy. All procedures were performed using a high-frequency electrosurgical unit (VIO300D; Erbe Elektromedizin, Tübingen, Germany). First, the target lesion border was marked using the tip of a 10-mm snare (Captivator II; Boston Scientific, Marlborough, Massachusetts, United States) in the soft coagulation mode (effect 3, 40W). Regarding the types of OTSCs used in the EMRO procedure, the traumatic (t) type for organs with thin walls was introduced. Then, the upper gastrointestinal endoscope was mounted with a 9t (11/6t) OTSC (9t, Japanese notation; 11/6t, overseas notation). The lesion, including the markings, was sufficiently suctioned into the applicator cap. The OTSC was successfully deployed outside the markings, creating a target lesion pseudo-polyp. Finally, the lesion was resected en bloc above the OTSC with a snare, using the endocut mode (endocut Q, effect 3, duration 1, interval 3). Hemostasis for procedural or delayed bleeding was achieved by setting the tip of the snare or hemostatic forceps using the soft coagulation mode (effect 4, 60W). On the second day after the EMRO procedure, all patients routinely underwent a second endoscopy to detect any delayed bleeding or perforation (▶ Fig.3, ▶ Video 1).

**Follow-up**

All patients were hospitalized after EMRO for 2 days according to the routine followed in our institution. Regarding the protocol criteria, oral intake of regular food was resumed on the day after EMRO. Proton pump inhibitors (rabeprazole 20 mg/day, lansoprazole 30 mg/day, or esomeprazole 20 mg/day) were administered for 2 weeks starting on the day of the procedure. To evaluate recurrences, patients underwent a first follow-up endoscopy at 6 months after EMRO. Thereafter, endoscopic follow-up was performed at 12-month intervals. If a residual tumor was suspected, a biopsy was performed, and the tissue obtained was examined histologically.

**Outcome measurements**

Primary outcomes were the rates of en bloc and R0 resection (defined as when both the lateral and vertical margins of the specimen were found to be histologically free of tumor cells), prevalence of post-EMRO AEs, as well as intraoperative perforation, delayed perforation, and delayed bleeding rates. Delayed bleeding was diagnosed as overt bleeding occurring within 14 days after EMRO and requiring an endoscopic hemostatic procedure using hemostatic forceps. Secondary outcomes were procedure time (defined as the time from when the endoscope with OTSC was inserted into the patient’s body to when the endoscope was removed); number of OTSC misplacement cases; pathological resected specimen/tumor size; invasion depth of tumor; pathological tumor type as G1, G2, or G3; and pathological resection depth. Theoretically, the resection depth achievable with EMRO can be classified into three categories according to differences in the layers of the resected gastrointestinal wall. Resection with a vertical margin including a substantial portion of the submucosal layer was termed deep submucosal resection (DSMR); resection with a vertical margin...
including the muscle layer was referred to as muscularis resection (MR); and resection with a vertical margin, including the serosa, was termed full-thickness resection (FTR). All specimens were subjected to pathological examinations. Quantitative data are expressed as medians and interquartile ranges. All analyses were performed using SPSS, version 11.0 (SPSS Inc., Chicago, Illinois, United States).

Results

Patient and lesion characteristics

All 13 patients (7 men; median age, 74 years) with 14 DNets ≤ 10 mm underwent EMRO during the study period. None of the patients were taking antithrombotic agents.

The patients’ clinicopathological and lesion characteristics are summarized in Table 1. Tumors were predominantly located in the bulb (10/14, 71.4%). The median tumor size was 6 mm (range 4 to 10).
Therapeutic outcomes

The treatment outcomes of 14 DNETs are summarized in Table 2. The median procedure time was 15 minutes (range 10 to 18). During EMRO, no OTSC misplacements in target lesions occurred. The median pathological resected specimen size was 10 mm (range 8 to 11), and the median pathological resected tumor size was 6 mm (range 3 to 8).

The final pathological diagnosis of tumors revealed that all lesions invaded the submucosal layer, with a histological diagnosis of NET G1 for all 14 lesions. En bloc and R0 resection rates were 100% (14/14) and 92.9% (13/14), respectively. In one case in which R0 resection could not be achieved, the vertical margin was pathologically diagnosed as inconclusive. Another case had lymphovascular invasion and, thus, additional surgical resection was recommended. However, the patient insisted on continued observation. We, therefore, decided to carefully perform a follow-up endoscopy and abdominal CT every 6 months. No local recurrence or distant metastasis was noted during the 36 months after resection.

5/14 cases were categorized as MR (Fig. 4), whereas no case was categorized as FTR. The aforementioned case wherein the vertical margin was pathologically diagnosed as inconclusive was categorized as DSMR.

Table 2 Short-term outcomes of EMRO for duodenal neuroendocrine tumors.

| Outcome                                      | Value |
|----------------------------------------------|-------|
| Procedure time (min), median (range)         | 15 (10–18) |
| OTSC misplacement, n (%)                     | 0 (0) |
| Pathological resected specimen size (mm), median (range) | 10 (8–11) |
| Pathological tumor size (mm), median (range) | 6 (3–8) |
| Invasion depth, n (%)                         |       |
| Submucosal layer                             | 14 (100) |
| Pathological type, n (%)                     |       |
| NET G1                                       | 14 (100) |
| En bloc resection rate, n (%)                 | 14/14 (100) |
| R0 resection rate, n (%)                      | 13/14 (92.9) |
| Lateral margin positive, n (%)                | 0 (0) |
| Vertical margin positive, n (%)               | 0 (0) |
| Inconclusive, n (%)                           | 1 (7.1) |
| Lymphovascular invasion, n (%)                | 1 (7.1) |
| Pathological resection depth, n (%)           |       |
| Deep submucosal resection                    | 9 (64.3) |
| Muscularis resection                          | 5 (35.7) |
| Full-thickness resection                      | 0 (0) |
| Intraoperative perforation, n (%)             | 0 (0) |
| Delayed perforation, n (%)                    | 0 (0) |
| Delayed bleeding, n (%)                       | 2 (14.3) |
| Follow-up period (months), median (range)     | 12 (7–36) |
| Patients who underwent first follow-up endoscopy, n (%) | 13 (100) |
| Local recurrence, n (%)                       | 0 (0) |
| OTSC retention in place at 6 months, n (%)    | 2 (14.3) |

R0 resection was achieved when both the lateral and vertical margins of the specimen were found to be histologically free of tumor cells. Procedure time was defined as the time from insertion of the endoscope with OTSC into the patient’s body to retrieval of the endoscope. OTSC misplacement was defined as deployment of the OTSC just onto target lesions, not outside the lesions, during the EMRO procedure. Final pathological assessments were performed according to the classification system of the World Health Organization. Delayed bleeding was diagnosed as overt bleeding occurring within 14 days after EMRO and requiring an endoscopic hemostatic procedure using hemostatic forceps. Patients underwent a first follow-up endoscopy at 6 months after EMRO. Thereafter, endoscopic follow-up was performed at 12-month intervals. If residual tumor was suspected, a biopsy was performed, and the tissue obtained was examined histologically. EMRO, endoscopic muscularis resection with OTSC; NET, neuroendocrine tumor; OTSC, over-the-scope clip.

Table 1 Clinical characteristics of the enrolled patients and characteristics of the duodenal neuroendocrine tumors.

| Characteristic                                 | Value |
|-----------------------------------------------|-------|
| Sex, n (%)                                    |       |
| Male                                          | 7 (53.8) |
| Female                                        | 6 (46.2) |
| Age (years), median (range)                   | 74 (58–80) |
| Consumption of antithrombotic agents, n (%)   | 0 (0) |
| Location, n (%)                               |       |
| Bulb                                          | 10 (71.4) |
| Descending part                               | 4 (28.6) |
| Tumor size (mm), median (range)               | 6 (4–10) |

EMRO, endoscopic muscularis resection with over-the-scope clip; NET, neuroendocrine tumor.
There was no incidence of intraoperative or delayed perforation. Moreover, delayed bleeding occurred in two (14.3%, 2/14) patients, which was detected during the second endoscopic examination performed on the second day after EMRO. Both of these patients had no symptoms and bleeding in the mucosal layer. In one case of perforation occurred after endoscopic full-thickness resection (EFTR) using a different type of OTSC than the one we used in this study. Because perforation can occur in EMRO, it is necessary to cut the lesion instantly using the endoscope. However, from a safety perspective, coagulation should be kept to a minimal extent because perforation due to thermal damage to the duodenal mucosa. Fortunately, no cases of delayed perforation were observed after endoscopic treatment using OTSC with coagulation, in the present study, or in our previous report [12] or any other reports. However, from a safety perspective, coagulation should be kept to the minimum required and direct coagulation with the OTSC and at high-frequency setting should be avoided. Otherwise, additional clipping of the mucosal defect within the OTSC after EMRO is also considered one of the methods to prevent delayed bleeding. However, we have tried it in several cases, but it failed because the clips were repelled by the OTSC.

Recently, a dedicated FTR device (FTRD; Ovesco Endoscopy AG) was made commercially available for mainly colorectal EFTR in Europe and the United States [21–23]. However, this device has not yet been approved for use in Japan. Thus, we
could not consider FTRD and used a commercially available OTSC for endoscopic resection of the duodenal lesions. In the meta-analysis by Brewer et al. regarding FTR using OTSC and FTRD, a high overall R0 resection rate was observed (81% for upper gastrointestinal subepithelial lesions) [24]. Similarly, in our study, the R0 resection rate was 92.9%. Thus, EMRO has been shown to be available for endoscopic resection of subepithelial lesions, such as DNETs.

The EMRO also has some disadvantages. First, the cost-effectiveness should be considered. A single OTSC costs approximately $800 or €600. Therefore, EMRO costs more than other conventional endoscopic resections. Currently, the use of OTSC for endoscopic resection is off-label, at least in Japan. Therefore, the medical fee points are calculated as a conventional EMR for duodenal tumors and the cost of the OTSC is paid by the hospital. Second, once an OTSC is placed inappropriately, such as just onto the target lesion, it is difficult to continue the resection. In our study, there were no OTSC misplacements. Currently, some OTSC removal methods, using clip cutting devices, have been reported, including: argon plasma coagulation [25]; the Nd:YAG laser [26]; and the remOVE system (DC Cutter; Ovesco Endoscopy) [27]. Among the three cutting devices, the remOVE system has been reported to be the safest and most effective in the clinical studies. However, this device has not yet been approved for use in Japan. It is expected to be introduced in clinical practice as soon as possible. Use of other removal methods, such as grasping forceps [28], EMR/ESD [29] and ice-cold saline solution [30], also have been reported. The safety and efficacy of these methods are uncertain because they have been described in only a few cases; moreover, the use of these methods is not recommended because they can cause new severe AEs [31]. Considering the above, intentional removal of an OTSC is not realistic; for this reason, sufficient preoperative simulation of OTSC deployment is recommended, as well as limitation of the target to only lesions in which the OTSC can be reliably deployed. Third, it is technically very difficult to perform repeat endoscopic resection of residual and recurrent lesions that are located within the retained OTSC. In our study, the OTSC was retained in 14.3% of the lesions. If the OTSC is removed naturally or by the aforementioned removal methods, residual and recurrent lesions can be resected with EMRO [32]; if they cannot be removed, surgical resection may be considered [21].

The limitations of our study should be acknowledged. First, this was a single-center study with a small sample size, retrospective design, and lack of a control group, which might have introduced a selection bias. Second, all procedures were performed by a single experienced endoscopist and the outcomes could not be directly generalized. Third, this study had a short follow-up period and, thus, long-term follow-up outcomes are not available. Thus, prospective, multicenter, randomized controlled trials with larger sample sizes are warranted to establish the clinical usefulness of EMRO, to fully confirm its safety and effectiveness, and to investigate its long-term outcomes.

Conclusion
EMRO can be performed safely by an experienced endoscopist on small DNETs (≤10 mm). Further comparative studies are required to evaluate the safety and efficacy of EMRO compared to other endoscopic resection techniques.

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Competing interests
The authors declare that they have no conflict of interest.

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