

# Resectability of Small Duodenal Tumors: A Randomized Controlled Trial Comparing Underwater Endoscopic Mucosal Resection and Cold Snare Polypectomy

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**INTRODUCTION:** Underwater endoscopic mucosal resection (UEMR) and cold snare polypectomy (CSP) are novel endoscopic procedures for superficial nonampullary duodenal epithelial tumors (SNADET). However, consensus on how to use both procedures appropriately has not been established. In this study, we evaluated treatment outcomes of both procedures, including resectability.

**METHODS:** In this single-center randomized controlled study conducted between January 2020 and June 2022, patients with SNADET  $\leq 12$  mm were randomly allocated to UEMR and CSP groups. The primary end point was sufficient vertical R0 resection (SVRO), which was defined as R0 resection including a sufficient submucosal layer. We compared treatment outcomes including SVRO rate between groups.

**RESULTS:** The SVRO rate was significantly higher in the UEMR group than in the CSP group (65.6% vs 41.5%,  $P = 0.01$ ). By contrast, the R0 resection rate was not significantly different between study groups (70.3% vs 61.5%,  $P = 0.29$ ). The submucosal layer thickness was significantly greater in the UEMR group than in the CSP group (median 546 [range, 309–833]  $\mu\text{m}$  vs 69 [0–295]  $\mu\text{m}$ ,  $P < 0.01$ ). CSP had a shorter total procedure time (median 12 [range, 8–16] min vs 1 [1–3] min,  $P < 0.01$ ) and fewer total bleeding events (9.4% vs 1.5%,  $P = 0.06$ ).

**DISCUSSION:** UEMR has superior vertical resectability compared with CSP, but CSP has a shorter procedure time and fewer bleeding events. Although CSP is preferable for most small SNADET, UEMR should be selected for lesions that cannot be definitively diagnosed as mucosal low-grade neoplasias.

**KEYWORDS:** cold snare polypectomy; resectability; SNADET; superficial nonampullary duodenal epithelial tumor; underwater endoscopic mucosal resection

*Am J Gastroenterol* 2024;119:856–863. <https://doi.org/10.14309/ajg.0000000000002634>

## INTRODUCTION

Superficial nonampullary duodenal epithelial tumors (SNADET) were previously considered very rare; however, the likelihood of detecting SNADET has increased with advancements in endoscopic techniques and increased vigilance (1,2). SNADET, a clinical diagnosis including adenomas, intramucosal carcinomas, and submucosal invasive carcinomas, requires reliable treatment (1).

Surgical procedures such as pancreatoduodenectomy are treatment options for duodenal carcinoma but are associated with considerable morbidity and mortality of 30%–40% and 1%–4%, respectively (3–5). Endoscopic treatment is a reasonable alternative because it is minimally invasive, can preserve organs, and can maintain the patient's postoperative quality of life. Endoscopic treatment such as endoscopic submucosal dissection (ESD) commonly performed for large lesions (6,7) is technically

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Received August 20, 2023; accepted November 10, 2023; published online December 22, 2023

challenging and often causes severe adverse events (8–11). Therefore, resection using a snare, which is technically relatively easy, is commonly preferred for small lesions. Thus, in SNADET, it is very important to select the appropriate procedure for each lesion characteristic.

As a representative procedure using snare, endoscopic mucosal resection (EMR) is an acceptable treatment option for small lesions (12–15). However, EMR is challenging in cases with biopsy-induced fibrosis or sublesional Brunner's glands because this often leads to nonlifting tumors (12,16,17). Because preoperative diagnosis is relatively difficult in SNADET, biopsies are often performed preoperatively. Hence, fibrotic lesions after preoperative SNADET biopsy can be encountered (18).

To overcome such problems, underwater EMR (UEMR) has been proposed and has recently become popular because it is considered safe and effective (19–25). Regarding colorectal lesions, UEMR, which does not require injection, has already been reported to be useful for residual or recurrent lesions with nonlifting following injection (26). Kiguchi et al (24) reported that in SNADET, UEMR is less likely than EMR to be converted to ESD due to nonlifting or poor maneuverability. Furthermore, Okimoto et al reported that UEMR has a significantly higher R0 resection rate than EMR and a lower risk of delayed bleeding (27,28).

However, cold snare polypectomy (CSP), the standard treatment for nonpedunculated colorectal polyps <10 mm, is also becoming popular as a treatment for small SNADET, and its efficacy and safety have been reported (29,30). Maruoka et al (31) report that CSP is safe and effective, especially for SNADET  $\leq 6$  mm.

Thus, UEMR and CSP are both effective procedures for relatively small SNADET. However, direct comparisons of their effectiveness have not been reported yet. In evaluating the effectiveness of these 2 procedures, we focused on pathological resectability. Reliable resection including the submucosal layer is very important not only for curative treatment but also for the accurate pathological diagnosis and appropriate judgment regarding the need for additional treatment because submucosal invasion might be underestimated in resected specimens without submucosal layer. Even for small SNADET that are resectable by UEMR or CSP, it would be desirable to obtain specimens that will enable appropriate judgment regarding the need for additional treatment. Therefore, we conducted a randomized controlled trial to compare the effectiveness of these 2 procedures including their resectability with pathological analysis.

## METHODS

### Study design

This single-center randomized controlled trial was performed in accordance with the 2008 version of the Declaration of Helsinki. The study protocol was approved by the Keio University School of Medicine Ethics Committee (No. 20190147; November 25, 2019). All patients were sufficiently informed about the trial, and consent in writing was obtained. The study was registered in the University Hospital Medical Network Clinical Trials Registry (UMIN000039061). All authors had access to the study data and reviewed and approved the final manuscript.

### Patient population

Eligibility criteria were patients aged 20 years or older scheduled for snare-based endoscopic resection of small SNADET with

suspected mucosal low-grade neoplasia equivalent to Vienna classification category 3. Because a correlation has been reported between tumor diameter and carcinoma rate in duodenal tumors, we defined a small lesion as a lesion below the cutoff value of 12 mm based on its receiver operating characteristic curve (32). Lesion size was measured by comparison with an open biopsy forceps of 4 mm. It has been reported that the malignancy of lesions with intestinal phenotype is lower than that with gastric phenotype, and the lesion phenotype is to some extent predictable based on endoscopic findings (33). Because SNADET with white opaque substance (WOS) are presumably mucosal low-grade neoplasia, we mainly estimated the malignancy potential of SNADET based on the presence of WOS (32). The endoscopic diagnosis was based on white light imaging, indigo carmine spray, and magnified narrow-band or blue laser imaging. In patients with multiple lesions, only the largest lesion scheduled for snare treatment was registered to maintain the independence and distribution of analyzed units.

Exclusion criteria were familial adenomatous polyposis or hereditary nonpolyposis colorectal carcinoma, previous surgery to the upper gastrointestinal tract, antithrombotic drug contraindications according to the guidelines for gastrointestinal endoscopy, vital organ failure, and other reasons considered to be inappropriate for enrollment by the doctors in our department.

### Operators

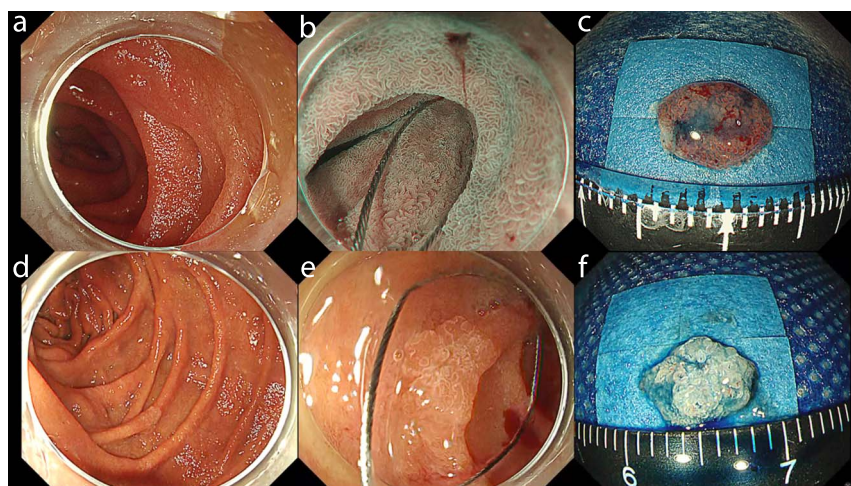
All operators received specialized training in the detailed evaluation and treatment of SNADET in our department. Operators who had encountered  $\geq 300$  or <300 lesion ESDs were considered experts ( $n = 5$ ) and nonexperts ( $n = 8$ ), respectively.

### Endoscopic procedures

All procedures were conducted using the EVIS-X1 endoscopy system (Olympus Medical Systems, Tokyo, Japan). All operators used a high-vision therapeutic endoscope with a water jet function (GIF-H290T or GIF-Q260J; Olympus Medical Systems) and a snare (SnareMaster 10 mm or SnareMaster Plus 10 mm, Olympus Medical Systems; Captivator Cold 10 mm or Captivator II 13 mm; Boston Scientific, Marlborough, MA) depending on lesion size and shape. The choice of the scope and snare was determined by the operators' preference, and all operators attempted initial *en bloc* resection.

The UEMR procedure included (i) detection of the lesion under CO<sub>2</sub> insufflation, (ii) complete deflation of the duodenal lumen, (iii) total immersion of the lumen with saline using a mechanical water pump (OFR-2; Olympus Medical Systems), (iv) snaring of the lesion and surrounding mucosa, and (v) resection using electrical energizing (Figure 1). The snare was powered by a high-frequency electrosurgical unit (VIO 3; ERBE Elektromedizin, Tübingen, Germany), which supported dissection (endo cut Q function, effect 1.0) and hemostasis with the snare tip (forced coagulation function, effect 2.0).

The CSP procedure included (i) detection of the lesion under CO<sub>2</sub> insufflation, (ii) snaring of the lesion and surrounding mucosa, and (iii) resection without electrical energizing (Figure 1). Apparent or suspected residual lesions were resected using the same procedure until complete removal was achieved. Resected wounds were closed with clips (EZ clip; Olympus Medical Systems) according to the operator's preference. To prevent specimen fragmentation due to strong suction forces, the resected specimen was collected by withdrawing the scope with suction



**Figure 1.** CSP and UEMR procedures and resected specimens. (a) A white light image of a lesion in the descending part of the duodenum before UEMR. (b) NBI during snaring in UEMR. Underwater snaring was performed while confirming the extent of the lesion with NBI. Resection was performed using electrical energizing. (c) A white light image of the resected specimen after UEMR with indigo carmine spraying. R0 resection was achieved. (d) A white light image of a lesion in the descending part of the duodenum before CSP. (e) A white light image during snaring in CSP. Snaring was performed to ensure an adequate normal mucosa, and resection was performed without electrical energizing. (f) A white light image of the resected specimen after CSP with indigo carmine spraying. R0 resection was achieved. CSP, cold snare polypectomy; NBI, narrow-band imaging; UEMR, underwater endoscopic mucosal resection.

while the device used for resection was retained in the delivery channel of the endoscope.

### Pathological diagnosis

The collected specimens were laid out on filter paper and fixed with 10% formalin. Afterward, the specimens were sent to the Department of Pathology for histological assessment and divided into sections at 2-mm intervals for pathological evaluation. A pathologist specialized in gastrointestinal disorders evaluated all tumors based on the Vienna classification (34).

### Pathological image evaluation

We analyzed all cases using ImageJ (National Institutes of Health, Bethesda, MD) based on the largest tissue section of each lesion. We evaluated whether specimens included the entire muscularis mucosa and submucosal layer beneath the lesion. For specimens that included the submucosa, we determined the submucosal layer thickness. The submucosal area and length of the muscularis mucosa were measured using ImageJ, and submucosal thickness was calculated as the submucosal area divided by muscularis mucosa length (Figure 2).

### Randomization and masking

Allocation tables were created using Excel 2016 (Microsoft, Redmond, WA). Eligible patients were 1:1 randomly assigned to the CSP or UEMR group using simple randomization. Stratified or allocation factors were not set for randomization. Patients were masked to their assigned group during the endoscopic procedure. Operators were not blinded; they were informed immediately before the procedure which group the patient was allocated to.

### Outcomes

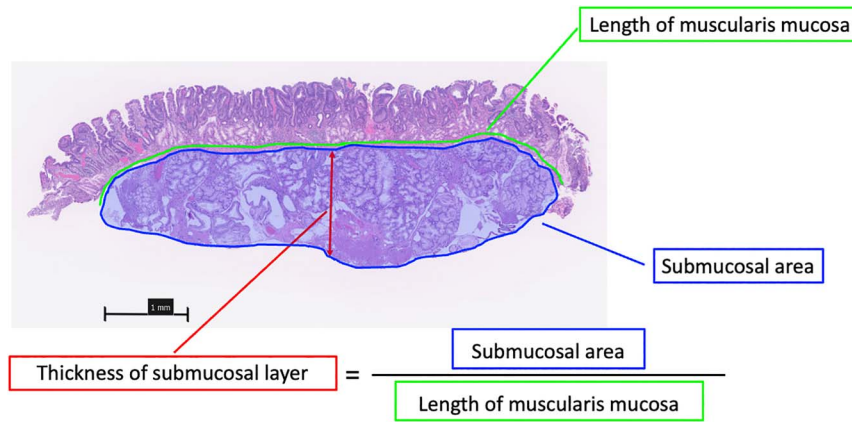
A sufficient vertical R0 resection (SVR0) rate was the primary outcome of this study. R0 resection including a sufficient submucosal layer beneath the entire lesion, regardless of layer thickness, was defined as SVR0. We considered SVR0 very

important and set it as the primary outcome because specimens that include the submucosal layer allow us not only to achieve curative treatment but also to perform accurate pathological diagnosis including invasion depth, even in carcinomas with submucosal invasion.

Secondary outcomes included *en bloc* resection rate, R0 resection rate, resection time, closure time, total procedure time, specimen size, fasting period, hospitalization period, adverse events, and local recurrence rate. *En bloc* resection was defined as complete endoscopic resection of the lesion in 1 piece. R0 resection was defined as *en bloc* resection with a histologically confirmed negative resection margin. Resection time was measured from the time of snare delivery until complete resection was achieved. Closure time was measured from the time of clip forceps delivery until finishing the suture. Total procedure time was defined as the sum of resection time and closure time. Adverse events were subdivided into 7 items (muscular layer injury, intraprocedural perforation, delayed perforation, total bleeding, intraprocedural bleeding, delayed bleeding, and aspiration pneumonia). Intraprocedural perforation was defined as visible peritoneal fat on the endoscopic image. Delayed perforation was defined as abdominal pain with evidence of air or luminal contents outside the gastrointestinal tract on abdominal computed tomography. Intraprocedural bleeding was defined as bleeding requiring hemostasis. Delayed bleeding was defined as any hematemesis or hemorrhage with decreased hemoglobin that required endoscopic hemostasis. Total bleeding was defined as the sum of intraprocedural bleeding and delayed bleeding. Local recurrence was assessed endoscopically 6 months after resection.

### Sample size

In a previous retrospective observational study at our institution, the R0 resection rate of UEMR for SNADET was 67% (24). Because the SVR0 rate was assumed to be lower than this rate, the SVR0 rate of UEMR was estimated to be 60%. Regarding CSP, the



**Figure 2.** Pathological image evaluation. The length of the muscularis mucosa and the submucosal area were measured using ImageJ. Submucosal thickness was defined as the submucosal area divided by muscularis mucosa length.

R0 rate for SNADET has been reported to be 68% (31). Another CSP study on colorectal polyps reported that the resection rate of small colorectal polyps including the submucosal layer was 24% (35). Considering these reports, we estimated the SVR0 rate of CSP as 35%. Based on these rates with overall 2-sided  $\alpha$  and  $\beta$  errors of 0.05 and 0.20, respectively, the required sample size was 130 patients, allowing for an approximate 10% dropout rate.

### Statistical analysis

We compared the clinical outcomes between the UEMR and CSP groups. The  $\chi^2$  and Fisher exact tests were used for comparisons of categorical variables. The Wilcoxon rank sum test was used for comparisons of continuous variables. All statistical analyses were performed using JMP version 16.2.0 (SAS Institute, Cary, NC).  $P < 0.05$  was considered statistically significant.

## RESULTS

### Participant flow

From October 2020 to June 2022, 174 patients presented SNADET  $\leq 12$  mm, which were suspected to be mucosal low-grade neoplasia. After excluding patients with familial adenomatous

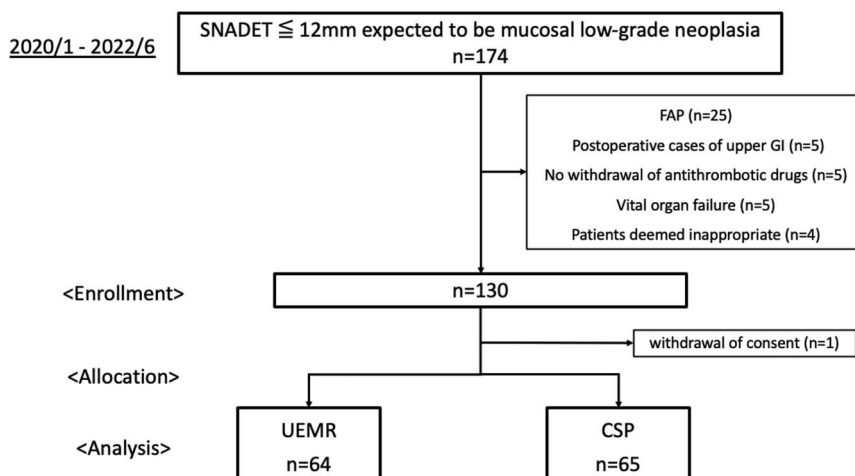
polyposis ( $n = 25$ ), those with prior upper gastrointestinal surgery ( $n = 5$ ), those who could not discontinue antithrombotic drugs ( $n = 5$ ), those who had vital organ failure ( $n = 5$ ), and those who were judged inappropriate for enrollment ( $n = 4$ ), 130 patients were enrolled. After the exclusion of one patient who withdrew consent, 129 patients were analyzed. Patients were randomly allocated to the UEMR ( $n = 64$ ) and CSP ( $n = 65$ ) groups (Figure 3).

### Participant and lesion characteristics

Characteristics of the 129 patients are summarized in Table 1. Although the median patient age was significantly higher in the UEMR group, all other patient characteristics were balanced between the 2 groups. The median lesion size was 7 mm in the UEMR group and 6 mm in the CSP group. In both groups, nonexperts treated approximately 80% of patients.

### Sufficient vertical R0 resection

The SVR0 rates in both groups are shown in Figure 4. In the UEMR group, the SVR0 rate was 65.6% (42/64). By contrast, the SVR0 rate in the CSP group was 41.5% (27/65). The SVR0 rate



**Figure 3.** Patient flow in this study. CSP, cold snare polypectomy; FAP, familial adenomatous polyposis; SNADET, superficial nonampullary duodenal epithelial tumor; UEMR, underwater endoscopic mucosal resection.

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**Table 1.** Clinical characteristics of study population (n = 129)

|                                           | UEMR (n = 64) | CSP (n = 65) | P value           |
|-------------------------------------------|---------------|--------------|-------------------|
| Age                                       |               |              |                   |
| Median [IQR], yr                          | 65 [57–73]    | 58 [50–67]   | 0.01 <sup>a</sup> |
| Sex                                       |               |              |                   |
| Male, n (%)                               | 39 (60.9%)    | 44 (67.7%)   | 0.47              |
| Lesion size                               |               |              |                   |
| Median [IQR], mm                          | 7 [5–8]       | 6 [5–10]     | 0.77              |
| Macroscopic type, n (%)                   |               |              |                   |
| O-IIa                                     | 38 (59.4%)    | 41 (63.1%)   | 0.78              |
| O-IIc                                     | 24 (37.5%)    | 21 (32.3%)   |                   |
| Others                                    | 2 (3.1%)      | 3 (4.6%)     |                   |
| Location, n (%)                           |               |              |                   |
| Duodenal bulb ~ superior duodenal angle   | 7 (10.9%)     | 7 (10.7%)    | 0.86              |
| Descending part                           | 47 (73.4%)    | 50 (76.9%)   |                   |
| Inferior duodenal angle ~ horizontal part | 10 (15.6%)    | 8 (12.3%)    |                   |
| Occupied circumference, 0%–25%, n (%)     | 64 (100.0%)   | 65 (100.0%)  | —                 |
| Preoperative biopsy, n (%)                | 18 (28.1%)    | 25 (38.5%)   | 0.26              |
| Operator Nonexpert, n (%)                 | 51 (79.7%)    | 55 (84.6%)   | 0.46              |

CSP, cold snare polypectomy; IQR, interquartile range; UEMR, underwater endoscopic mucosal resection.  
<sup>a</sup>Statistically significant.

was significantly higher in the UEMR group than in the CSP group ( $P = 0.01$ ).

**Treatment outcomes and clinical courses**

Treatment outcomes and clinical courses in both groups are summarized in Table 2. In both groups, *en bloc* resection was achieved at a high rate of > 90%. R0 resection rates did not significantly differ between the groups. Both resection and closure

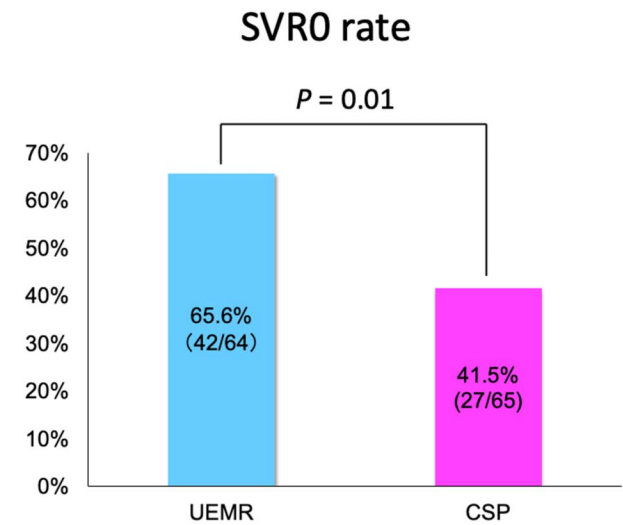
time were significantly longer in the UEMR group, and total treatment time was also significantly longer in this group. There were no significant group differences regarding fasting and hospitalization periods. Intraoperative and postoperative perforation did not occur in either group. Two cases of intraprocedural bleeding were recorded in the UEMR group, both of which were endoscopically terminated. More total bleedings occurred in the UEMR group without reaching significance. There was no group difference regarding other adverse events. Only 1 local recurrence was observed in the CSP group.

**Pathological image evaluation**

The results of pathological image evaluations in both groups are summarized in Table 3, and representative images are shown in Figure 5. The rate of lesions that had been resected with the entire muscularis mucosa and submucosal layer was significantly higher in the UEMR group than in the CSP group ( $P < 0.01$ ). The median submucosal layer thickness was also significantly higher in the UEMR group ( $P < 0.01$ ).

**DISCUSSION**

In this study, more resected specimens in the UEMR group contained sufficient submucosal layers compared with those in the CSP group. Although the R0 resection rate did not significantly differ between the study groups, the SVR0 rate was significantly higher in the UEMR group because R0 resection without submucosal layer was more frequent in the CSP group, i.e., many specimens contained only a very shallow layer. This indicates that UEMR has superior vertical resectability. Our findings mirror a previous report in colorectal polyps



**Figure 4.** SVR0 rates of the 2 study groups. CSP, cold snare polypectomy; SVR0, sufficient vertical R0 resection; UEMR, underwater endoscopic mucosal resection.

**Table 2. Treatment outcomes and clinical courses (n = 129)**

|                                           | UEMR (n = 64) | CSP (n = 65) | P value            |
|-------------------------------------------|---------------|--------------|--------------------|
| <i>En bloc</i> resection, n (%)           | 59 (92.2%)    | 62 (95.4%)   | 0.49               |
| R0 resection, n (%)                       | 45 (70.3%)    | 40 (61.5%)   | 0.29               |
| Resection time, median [IQR], min         | 4 [2–7]       | 1 [1–3]      | <0.01 <sup>a</sup> |
| Closure time, median [IQR], min           | 6 [5–9]       | 0 [0–0]      | <0.01 <sup>a</sup> |
| Total procedure time, median [IQR], min   | 12 [8–16]     | 1 [1–3]      | <0.01 <sup>a</sup> |
| Specimen size, median [IQR], min          | 10 [8–14]     | 10 [8–13]    | 0.93               |
| Fasting period, median [IQR], min         | 1 [1–1]       | 1 [1–1]      | 0.31               |
| Hospitalization period, median [IQR], min | 4 [4–4]       | 4 [4–4]      | 0.34               |
| Adverse events                            |               |              |                    |
| Muscular layer injury, n (%)              | 0 (0.0%)      | 0 (0.0%)     | —                  |
| Intraprocedural perforation, n (%)        | 0 (0.0%)      | 0 (0.0%)     | —                  |
| Delayed perforation, n (%)                | 0 (0.0%)      | 0 (0.0%)     | —                  |
| Total bleeding, n (%)                     | 6 (9.4%)      | 1 (1.5%)     | 0.06               |
| Intraprocedural bleeding, n (%)           | 2 (3.1%)      | 0 (0.0%)     | 0.24               |
| Delayed bleeding, n (%)                   | 4 (6.3%)      | 1 (1.5%)     | 0.21               |
| Aspiration pneumonia, n (%)               | 2 (3.1%)      | 3 (4.6%)     | 1.00               |
| Histological diagnosis                    |               |              |                    |
| Vienna classification                     |               |              |                    |
| Category 3                                | 47 (78.3%)    | 52 (82.5%)   | 0.46               |
| Category 4.1                              | 13 (21.7%)    | 10 (15.9%)   |                    |
| Category 4.2                              | 0 (0.0%)      | 1 (1.6%)     |                    |
| Beyond category 5.1                       | 0 (0.0%)      | 0 (0.0%)     |                    |
| Local recurrence, n (%)                   | 0 (0.0%)      | 1 (1.5%)     | 1.00               |

CSP, cold snare polypectomy; IQR, interquartile range; UEMR, underwater endoscopic mucosal resection.

<sup>a</sup>Statistically significant.

demonstrating that CSP results in shallower resection depth than hot snare polypectomy or UEMR (35,36). Moreover, the median thickness of the submucosal layer in the UEMR group (546  $\mu$ m) is highly indicative of sufficient resectability given the definitions of submucosal deep invasion for other gastrointestinal carcinomas (esophagus 200  $\mu$ m, stomach 500  $\mu$ m, and colon 1,000  $\mu$ m).

However, resection and total procedure time were significantly shorter in the CSP group than in the UEMR group,

although *en bloc* and R0 resection rates were equivalent in both study groups. Furthermore, although not significantly different, total bleeding events tended to be fewer in the CSP group. Had the sample size been larger, delayed bleeding might have become significantly more frequent in the UEMR group. These data suggest that CSP is a simple and safe procedure with a lateral resectability equivalent to that of UEMR.

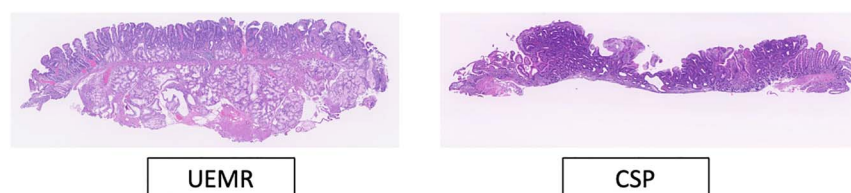
In addition, we need to consider the specific characteristics of SNADET. Although Nakayama et al (32) reported that the presence of WOS and lesion size are associated with lesion malignancy, the diagnostic criteria of SNADET are not fully established yet. We occasionally experience cases of invasive carcinoma (equivalent to Vienna classification category C5.2), even in small lesions (37). To achieve the best possible curative resection and pathological diagnosis including invasion depth, the indication for CSP should be carefully considered for lesions where mucosal high-grade neoplasia cannot be excluded because resecting only the mucosal layer may be insufficient for a pathological evaluation and submucosal invasion depth may be underestimated. By contrast, with a sufficient submucosal layer, the need for additional surgery can be appropriately determined. For such lesions, we recommend UEMR including the submucosal layer. For small SNADET with WOS, which can with high confidence be suspected to be mucosal low-grade neoplasias,

**Table 3. Outcomes of pathological image evaluation (n = 129)**

|                                                     | UEMR (n = 64) | CSP (n = 65) | P value            |
|-----------------------------------------------------|---------------|--------------|--------------------|
| Muscularis mucosa including, n (%)                  | 56 (87.5%)    | 43 (66.2%)   | <0.01 <sup>a</sup> |
| Submucosal layer including, n (%)                   | 56 (87.5%)    | 35 (53.8%)   | <0.01 <sup>a</sup> |
| Thickness of submucosal layer Median [IQR], $\mu$ m | 546 [309–833] | 69 [0–295]   | <0.01 <sup>a</sup> |

CSP, cold snare polypectomy; IQR, interquartile range; UEMR, underwater endoscopic mucosal resection.

<sup>a</sup>Statistically significant.



**Figure 5.** Representative pathological images. CSP, cold snare polypectomy; UEMR, underwater endoscopic mucosal resection.

CSP is considered the preferable treatment because of its adequate lateral resectability, short procedure time, relatively lower total bleeding, and simplicity.

The strengths of our study are its randomized controlled trial design and the novelty of its focus. Although previous reports compared UEMR with EMR (24,27,28,38), none compared UEMR with CSP, which have recently become mainstream procedures for small SNADET. It should also be emphasized that the SVR0 rate was the primary outcome to evaluate vertical resectability, and the submucosal layer thickness was calculated in all cases as supportive data. As mentioned earlier, clear criteria for use of these 2 procedures are lacking, and the indications depend on the judgment of each institution and operator. Our study has shown a possible solution; we suggest how to use 2 procedures based on endoscopic lesion findings, with a sufficient understanding of the advantages and disadvantages of each procedure.

Our study also has several limitations. First, it was a single-center study. Our hospital is a high-volume center that has performed numerous diagnostic and therapeutic endoscopies for SNADET, and we consider many of our operators to be highly experienced in this field. Therefore, the results of this study may not be directly transferable to other hospitals. Second, patient characteristics differed because this study was designed with simple randomization. The median patient age differed by 7 years between groups, and we cannot completely rule out the possibility that this may have affected the results. Third, the operators were not blinded. Fourth, there may be a learning curve in CSP and UEMR techniques. Because these clinical data were obtained over approximately 2.5 years, we cannot deny the possibility that technical improvements during this period may have affected the treatment outcomes. Fifth, the calculated thickness of the submucosal layer (the submucosal layer area divided by the length of the muscularis mucosa) may differ from the actual thickness of the submucosal layer because the muscularis mucosa is not straight. Sixth, adverse events were insufficiently considered because the sample size was defined to evaluate SVR0.

In conclusion, this trial demonstrated that for small SNADET, UEMR had superior vertical resectability compared with CSP. However, CSP had fewer bleeding events, a shorter procedure time, and an R0 resection rate equivalent to UEMR. Although CSP is preferable for most small SNADET, UEMR should be selected for lesions that cannot be definitively diagnosed as mucosal low-grade neoplasias.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Motohiko Kato, MD, PhD.

**Specific author contributions:** Yo.Ki. and M.K.: study concept and design. Ku.M., A.N., M.S., D.M., Ko.M., K.I., T.M., Yo.Ku., M.M., Y.H., Yo.Ki., T.A., Y.T., S.K., N.M., T.S., K.T., T.K., N.Y., M.K.: acquisition of data and critical revision of the manuscript for

important intellectual content. Ku.M. and Ke.M.: statistical analysis. K.Y.: pathological diagnosis. M.S.: technical support. N.Y. and M.K.: study supervision. All authors approved the final draft submitted.

**Financial support:** None to report.

**Potential competing interests:** None to report.

**Trial registration:** The study was registered in the University Hospital Medical Network Clinical Trials Registry (UMIN000039061; <https://www.umin.ac.jp/>).

**Ethics statement:** This trial was performed in accordance with the 2008 version of the Declaration of Helsinki. The study protocol was approved by the Keio University School of Medicine Ethics Committee (No. 20190147; November 25, 2019). All patients provided written informed consent.

## Study Highlights

### WHAT IS KNOWN

- ✓ Superficial nonampullary duodenal epithelial tumors can be endoscopically removed.
- ✓ Underwater endoscopic mucosal resection (UEMR) and cold snare polypectomy (CSP) are 2 novel endoscopic procedures.

### WHAT IS NEW HERE

- ✓ For small superficial nonampullary duodenal epithelial tumors, UEMR had superior vertical resectability compared with CSP.
- ✓ CSP has a shorter procedure time and fewer bleeding events compared with UEMR.

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