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Safety of cold snare polypectomy for duodenal adenomas in familial adenomatous polyposis: a prospective exploratory study

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ABSTRACT

Background Cold snare polypectomy (CSP) to remove multiple duodenal adenomas (MDAs) in patients with familial adenomatous polyposis (FAP) could be an effective and less invasive method than more extensive surgery. The aim of the present study was to determine the safety of this procedure.

Methods This prospective exploratory study included 10 consecutive patients with FAP and MDAs who underwent CSP for as many as 50 duodenal adenomas. The primary outcome was the incidence of severe adverse events.

Results 10 patients were enrolled and underwent 332 CSPs from June 2016 to January 2017. The median procedure time was 33 minutes (range 25 – 53), and the median number of polyps removed during a single session was 35 (range 10 – 50). Most of the removed polyps were ≤ 10 mm. None of the 10 patients experienced a severe adverse event. One patient developed arterial bleeding during the procedure, but it was easily managed using hemoclips.

Conclusions CSP for MDAs in patients with FAP was safe. The long-term efficacy of this procedure should be investigated.

University Hospital Medical Network Clinical Trials Registry UMIN000022525
TRIAL REGISTRATION: Single-center, exploratory, prospective trial UMIN000022525 at http://www.umin.ac.jp.

Introduction

Duodenal adenomas occur in up to 90 % of patients with familial adenomatous polyposis (FAP) [1]. Patients with advanced-stage duodenal adenomas were found to have a high risk of developing duodenal cancer (7 % – 36 %) over a follow-up period of 7.6 – 10.0 years [2]. Duodenal cancer is a major cause of death in patients with FAP after preventive proctocolectomy [1]. Theoretically, although preventive duodenectomy is effective for patients with advanced-stage duodenal adenomas, it is quite complicated, especially after proctocolectomy [3]. Also, because desmoid tumor – another major cause of death in patients with FAP after preventive proctocolectomy – often develops after the surgery, less invasive and preventive interventions are expected to improve the prognosis of patients with FAP.

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We have found that cold snare polypectomy (CSP) is a feasible technique for removing multiple duodenal adenomas (MDAs) in patients with FAP [4]. In the present study, we evaluated the safety of this intervention.

Methods

A single-arm prospective exploratory study was conducted to assess the safety of CSP for MDAs in patients with FAP at a Japanese cancer referral center. The institutional review board approved the study protocol. Written informed consent was obtained from each participant before their enrollment in the study. The study was registered in the UMIN Clinical Trials Registry System (UMIN000022525).

Participants

Patients with FAP and Spigelman stage ≥I duodenal adenomas (▶ **Table 1**) who met all of the following criteria were eligible for inclusion in the study: age ≥20 years; Eastern Cooperative Oncology Group performance status 0–2; hemoglobin concentration ≥9 g/dL; platelet count ≥100 000 /mm^3; prothrombin index ≥70 %; provision of written informed consent.

The exclusion criteria were as follows: endoscopic diagnosis of invasive cancer; age ≥81 years; history of duodenal resection; corticosteroid treatment; treatment with anticoagulant or antiplatelet agents that could not be suspended according to the Japanese guidelines [5]; treatment with nonsteroidal anti-inflammatory drugs that could not be suspended beginning 7 days prior to duodenal CSP until 28 days afterward; major organ failure.

CSP procedure

All procedures were performed by two endoscopists (K.H., Y.T.), with the patients under intravenous sedation. Polyp size was estimated by comparing the polyp with a fully opened snare of known size. The CSP procedure was performed using a colonoscope (PCF-Q260JI; Olympus, Tokyo, Japan) or a gastroscope (GIF-Q260J; Olympus) with a disposable transparent attachment (D-201–11804; Olympus) mounted on the tip of the endoscope. Either of two thin, stiff polypectomy snares (9-mm Exacto cold snare; US Endoscopy, Mentor, Ohio, USA; or 10-mm Captivator II; Boston Scientific, Marlborough, Massachusetts, USA) was used.

CSP was performed without any submucosal injection. Treatment of up to 50 lesions and as many as possible within a 60-minute period was allowed during a single session. The procedure was also finished when there were no lesions to be removed.

The resection wounds were inspected after CSP to identify any deep injury and to confirm hemostasis (▶ **Video 1**). The resection depth was considered ideal when a mucosal pattern was lacking and submucosal tissue was identified. When spurting arterial bleeding was identified, hemostasis was achieved with endoclips (rather than thermal ablation) to avoid muscular injury that could lead to perforation of the thin duodenal wall. The event was regarded as immediate bleeding. Oozing was simply monitored, without any hemostatic procedure. Piecemeal CSP was identified when apparent polyp residue was found.

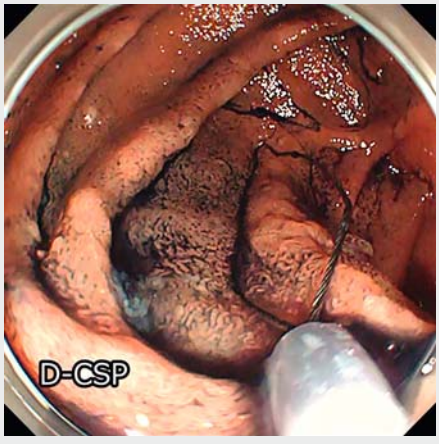
▶ **Table 1** Spigelman staging system for duodenal polyps in patients with familial adenomatous polyposis.

Points	1	2	3
Polyps, n	1–4	5–20	>20
Polyp size, mm	1–4	5–10	>10
Histological type	Tubular/hyperplastic/ inflammatory	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0, 0 points; stage I, 1–4 points; stage II, 5–6 points; stage III, 7–8 points; stage IV, 9–12 points.

The patients' characteristics, total number of removed polyps, the maximum sizes of removed polyps, location of the lesion (superior, descending, horizontal parts), and procedure time (from insertion to withdrawal of the endoscope) were recorded. No prophylactic procedures (e. g. suturing with hemoclips [6], tissue shielding with polyglycolic acid sheets and fibrin glue [7]) were recommended. No acid-suppressant agent was added for this treatment.

The patients fasted for 2 days after CSP. A liquid diet was started on postoperative day 2, and the diet was changed daily until it consisted of soft meals by postoperative day 5. In all, five to eight representative specimens, based on polyp size, were submitted for histological examination.



Video 1 Use of cold snare polypectomy to resect multiple duodenal adenomas in patient #10.
Online content viewable at:
https://doi.org/10.1055/s-0043-124765

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Measured outcomes

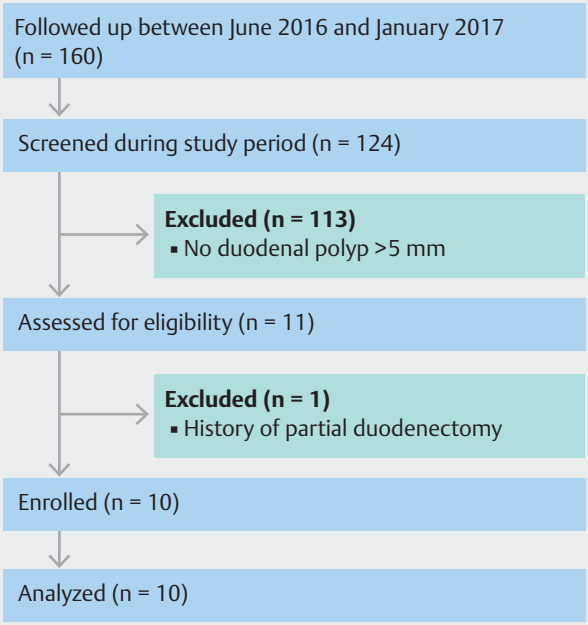
The primary outcome was a grade ≥ 3 adverse event as defined in the US National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE), which is a set of criteria for standardizing the classification of adverse events during cancer therapy [8] (▶ **Table 2**) during the first 28 days after CSP. The secondary outcomes were: arterial bleeding during the CSP procedure; (grade ≥ 1) adverse events stated in the NCI-CTCAE during the first 28 days after CSP; and the procedure time for a single session of CSP.

Follow-up and monitoring of adverse events

During hospitalization, adverse events were evaluated daily via patient interview and physical examination. All adverse events after discharge were verified by patient interviews at our outpatient department at 2 – 3 weeks and 2 – 3 months after discharge. The patients' background data were collected and sent to an independent data center prior to the procedure. Treatment outcomes and adverse events were also collected 1 week and 2 months after the procedure.

Sample size calculation and statistical analysis

This feasibility study included 10 patients, which was considered an appropriate number to demonstrate the safety of CSP because of the low prevalence of FAP. The outcomes were evaluated per patient and per lesion and are presented with their 95 % confidence interval (CI).



▶ **Fig. 1** Recruitment of patients with familial adenomatous polyposis seen at the Ishikawa Gastroenterological Medical Clinic and participant flow chart.

▶ **Table 2** US National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0*.

	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)	Grade 5 (Death)
Postoperative hemorrhage	No intervention	Endoscopic intervention	Transfusion or urgent endoscopic intervention	Life-threatening consequences	Death
Duodenal perforation	N/A	Medical intervention	Elective operative intervention	Urgent operative intervention	Death
Bloating	No change in oral intake	Decreased oral intake	N/A	N/A	N/A
Abdominal pain	Mild pain	Moderate pain; limiting instrumental activities of daily living	Severe pain; limiting self-care activities of daily living	N/A	N/A
Pneumonitis	No intervention	Medical intervention	Oxygen indicated	Urgent intervention (e. g. tracheotomy or intubation)	Death
Fever	38.0 – 39.0 °C (100.4 – 102.2 °F)	> 39.0 – 40.0 °C (102.3 – 104.0 °F)	> 40.0 °C (> 104.0 °F) for ≤ 24 hours	> 40.0 °C (> 104.0 °F) for > 24 hours	Death

N/A, not applicable.

* The NCI-CTCAE displays grades 1 to 5 with unique clinical descriptions of severity for each adverse event based on the following general guideline: Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to adverse events.

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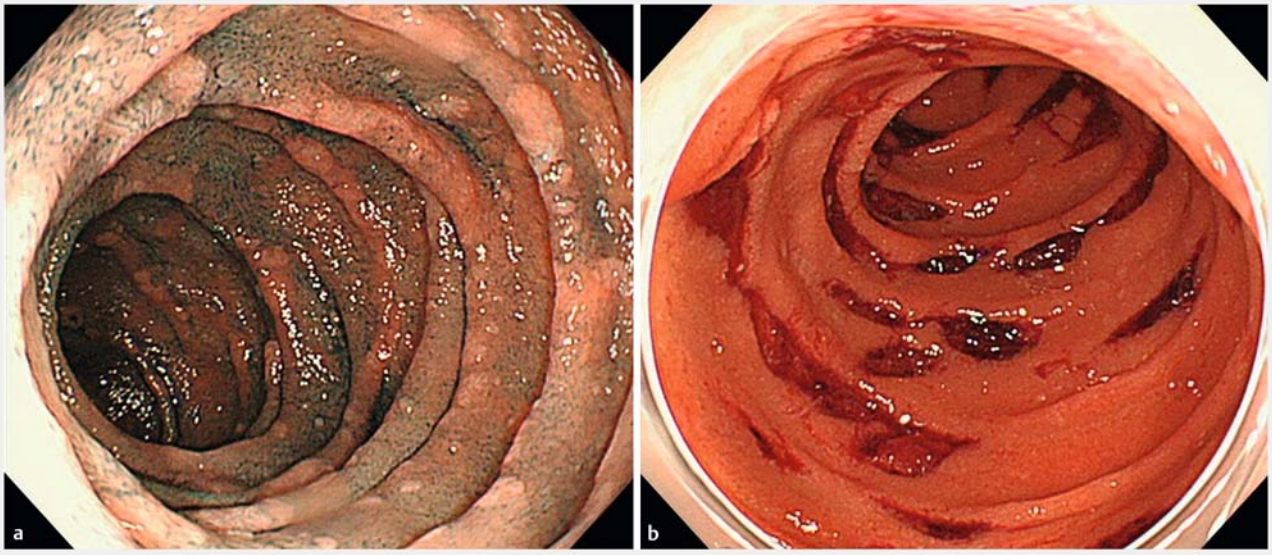


▶ **Fig. 2** Endoscopic images from patient #10: **a** before cold snare polypectomy (CSP) showing multiple duodenal adenomas in the second portion of the duodenum; **b** after CSP showing multiple resection wounds.

Results

Recruitment and participant flow

From June 2016 to January 2017, a total of 160 patients were followed up in the Ishikawa Gastroenterological Medical Clinic, and 124 patients were screened (▶ **Fig. 1**). The 11 patients with a duodenal adenoma > 5 mm were assessed for eligibility. One patient was excluded because of a history of partial duodenectomy. Therefore, 10 patients were enrolled and their outcomes were analyzed.

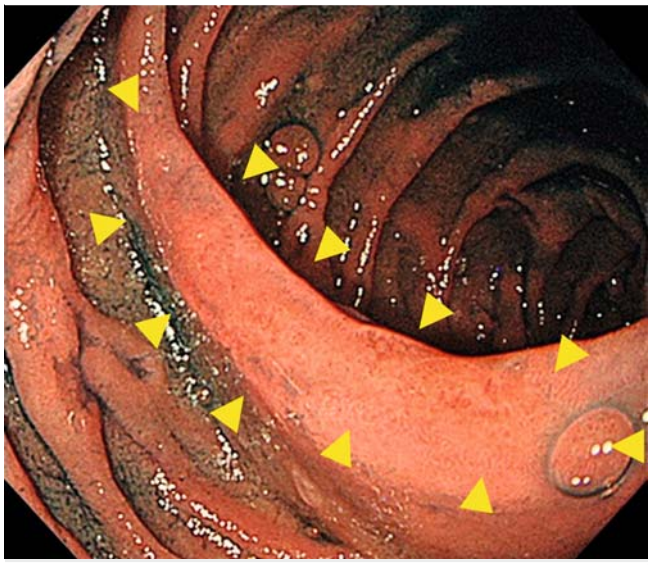
Baseline data

All 10 patients had MDAs (1 – 30 mm) (▶ **Fig. 2 a**) and were taking no acid-suppressant agents (▶ **Table 3**). CSP was performed for a total of 332 duodenal polyps (1 – 30 mm, median 35 lesions per patient) (▶ **Fig. 2 b**). Four lesions (1 %) in three patients were > 20 mm, and piecemeal CSP was performed on these (▶ **Fig. 3**). Five lesions (2 %) in four patients were 10 – 20 mm. The other 324 lesions (97 %) were < 10 mm.

A sampling of resected specimens showed no invasive carcinoma, and the Spigelman score did not change in any of the patients before and after CSP. Each patient underwent CSP once during the study period. The median procedure time for a single session was 33 minutes (range 25 – 53).

Outcomes

None of the 10 patients had a grade ≥ 3 adverse event (0 [95 %CI 0 – 0.3] per patient; 0 [95 %CI 0 – 0.01] per lesion) (▶ **Table 4**). One patient developed intraprocedural arterial bleeding during resection of a 9-mm adenoma (0.1 [95 %CI 0.003 – 0.45] per patient; 0.003 [95 %CI 0.0001 – 0.02] per lesion). The bleeding was easily managed using hemoclips. One patient developed grade 1 bloating. Another patient, from whom a 30-mm adenoma had been removed, developed grade 1 abdominal pain. None of the patients experienced a perforation or postoperative hemorrhage.



▶ **Fig. 3** Endoscopic image from patient #9 showing a lesion > 20 mm in size.

Discussion

No severe adverse events occurred in this study, allowing us to confirm the safety of CSP for MDA removal in patients with FAP. Currently, the endoscopic surveillance interval for patients with FAP is determined by the Spigelman stage. Watchful waiting has been recommended for patients with stages 0 – II, and

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▶ **Table 3** Characteristics of the 10 patients with familial adenomatous polyposis coli and duodenal adenomas > 5 mm who underwent cold snare polypectomy (CSP), their lesions, and treatment details.

Patient number	Sex; age, years	History of colectomy	History of ampullectomy	Location[1]	Polyps, n	Polyp size, mm	Histology	Dysplasia	Spigelman stage (score) before CSP	Snare type	Polyps resected, n	Procedure time, minutes
1	Male; 37	No	No	D1 – D3	> 20	4 – 12	Tubular	Moderate	IV (9)	Exacto	50	33
2	Female; 52	Yes	No	D1/D2 – D3	> 20	1 – 9	Tubular	Mild	III (7)	Exacto	29	26
3	Female; 33	Yes	No	D2 – D2/D3	> 20	2 – 12	Tubular	Severe	IV (10)	Exacto	16	28
4	Female; 47	Yes	No	D1/D2 – D3	> 20	1 – 4	Tubular	Mild	II (6)	Exacto	30	25
5	Male; 29	Yes	Yes	D1 – D3	> 20	1 – 5	Tubular	Mild	III (7)	Exacto	26	33
6	Male; 42	Yes	No	D1 – D3	> 20	1 – 30	Tubular	Moderate	IV (9)	Exacto	39	45
7	Female; 31	Yes	No	D1 – D3	> 20	2 – 12	Tubular	Severe	IV (10)	Exacto	10	46
8	Male; 45	No	No	D1/D2 – D3	> 20	2 – 20	Tubular	Severe	IV (10)	Exacto	39	53
9	Male; 35	No	No	D1 – D3	> 20	3 – 30	Tubular	Severe	IV (10)	Exacto/ Captivator II	43	48
10	Male; 42	Yes	No	D2 – D3	> 20	1 – 12	Tubular	Severe	IV (10)	Exacto	50	25

* D1, superior part (from pylorus to superior duodenal flexure); D2, descending part (from superior duodenal flexure to inferior duodenal flexure); D3, horizontal part (anal side of the inferior duodenal flexure); D1 /D2, D1 and D2 junction; D2 /D3, D2 and D3 junction.

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▶ **Table 4** Adverse events experienced during cold snare polypectomy (CSP) of duodenal adenomas and their management.

Patient number	Grade ≥ 3 adverse events	Arterial bleeding during CSP	Treatment for arterial bleeding	Grade ≥ 1 adverse events
1	No	No	–	No
2	No	Yes	Hemoclips	No
3	No	No	–	No
4	No	No	–	No
5	No	No	–	No
6	No	No	–	Bloating (Grade 1)
7	No	No	–	No
8	No	No	–	No
9	No	No	–	Abdominal pain (Grade 1)
10	No	No	–	No

endoscopic treatment has been suggested for patients with stage III because endoscopic treatment for duodenal lesions is associated with a high risk of adverse events [9, 10]. Prophylactic duodenectomy has been recommended for stage IV patients [10]. The estimated risk of developing stage IV disease by the age of 70 years is reportedly 20 % – 50 % [2] indicating that the current surveillance strategy involves waiting for progression of MDAs.

If secure endoscopic treatment for MDAs were available, these patients could however be treated aggressively to downstage their disease and avoid disease progression and the accompanying need for invasive surgery. We previously reported that no patients with FAP and MDAs developed CSP-related severe adverse events [4]. The current study confirmed the safety of our strategy and we believe that the use of CSP represents a paradigm shift for treating MDAs in patients with FAP.

The incidences of delayed bleeding and perforation are reportedly 0 % – 33 % and 0.6 % – 3 %, respectively, in patients undergoing duodenal endoscopic mucosal resection [11, 12]. As CSP is considered safer than conventional hot snare polypectomy [13], it is a promising treatment for duodenal polyps. Mild abdominal pain occurred only when 30-mm adenomas were removed. Therefore, careful observation might be needed when large adenomas are resected. In this study, no acid-suppressant agent was administered (as for ampullectomy), and no severe adverse events were observed. We believe an acid-suppressant agent is unnecessary for duodenal CSP.

The present study has some limitations. It was a single-center study involving a small number of patients and the efficacy of CSP was not evaluated. Therefore, we plan to investigate the short- and long-term safety and efficacy of our herein-described treatment strategy in a consecutive prospective trial. Additionally, most lesions removed in this study were small (< 10 mm), which might contribute to the excellent results.

In conclusion, CSP was safe for MDA resection in patients with FAP. The efficacy of CSP for MDAs will be assessed in an upcoming prospective study.

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Competing interests

None.

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