Annals of Gastroenterology (2024) **37,** 1-10

Results of the COLDWATER randomized controlled trial: enhanced performance of underwater cold snare polypectomy for colorectal polyps 5-10 mm, independent of endoscopist experience

Maria Zachou[a,b], Martha Nifora[c], Theodoros Androutsakos[d], Georgios Katsaras[e], Konstantinos Varytimiadis[f], Christina Zoumpouli[c], Panayiotis Karantanos[a], Efthimia Lalla[a], Georgios Mpetsios[a], Maria Panoutsakou[a], Roxana Stoica[a], Dionisia Thermou[g], Georgios Mavrogenis[h], Evangelia Ntikoudi[i], Nikolaos Nikiteas[b], Stavros Sougioultzis[d], Evangelos Kalaitzakis[j], Stilianos Kykalos[b]

"Laikon" General Hospital, Medical School, National and Kapodistrian University of Athens; "Sismanogleio" General Hospital, Athens; General Hospital of Pella–Hospital Unit of Edessa; "Evangelismos" General Hospital, Athens; "Hippocratio" General Hospital, Athens; Mediterraneo Hospital, Athens; Sotiria Thoracic Diseases Hospital, Athens; University Hospital of Heraklion, University of Crete, Heraklion, Greece

Abstract

Background The wide range of R0 resection rates (R0RR) and incomplete resection rates (IRR) observed with conventional cold snare polypectomy (CCSP) emphasizes the necessity for technique enhancement. The COLDWATER study aimed to compare underwater cold snare polypectomy (UCSP) to CCSP for 5-10-mm colorectal polyps, focusing on comprehensive histopathological evaluation, efficacy, and safety.

Methods This was a randomized, single-blind, controlled trial comparing UCSP to CCSP for non-pedunculated colorectal polyps of size 5-10 mm. The primary outcome was to report differences in the *muscularis mucosa* resection ratio. The secondary outcomes focused on differences in depth of excision, R0-RR, IRR, *en bloc* resection rate, adverse events, and recurrence rate.

Results The COLDWATER study found higher *muscularis mucosa* resection in UCSP (81.72±62.81% vs. CCSP: 72.33±22.33%, P=0.003) with comparable submucosa presence (UCSP: 16.6%, CCSP: 12.5%, P=0.25). UCSP showed better outcomes regarding IRR (3.5% vs. 8.5%, P=0.05) and *en bloc* resection (98% vs. 93.5%, P=0.04). In CCSP, expert endoscopists achieved higher R0RR than non-experts, while UCSP showed no significant difference in R0RR across endoscopist's experience levels.

Conclusions UCSP achieves a more extensive excision of the *muscularis mucosa* compared to CCSP, even though it does not attain a deeper excision. Additionally, UCSP shows a higher *en bloc* resection rate, with lower rates of IRR, and emerges as a promising technique for training inexperienced endoscopists in polypectomy, given its experience-independent success in achieving R0 resection.

Keywords Underwater cold snare polypectomy, underwater polypectomy, conventional cold snare polypectomy, *muscularis mucosa* resection ratio

Ann Gastroenterol 2024; 37 (XX): 1-10

Conflict of Interest: None

The study is registered with Clinical Trials.gov (NCT 05273697)

Correspondence to: Maria Zachou, MD, MSc, PhD candidate, Gastroenterology Resident, Department of Gastroenterology, "Sismanogleio" General Hospital, Athens, Greece, e-mail: zachou.maria@yahoo.com

Received 29 January 2024; accepted 23 April 2024; published online 14 June 2024

DOI: https://doi.org/10.20524/aog.2024.0889

Introduction

The European Society of Gastroenterology (ESGE) suggests using conventional cold snare polypectomy (CCSP) for 5-9-mm non-pedunculated colorectal polyps [1-2]. However, data for larger polyps (10-15 mm) is limited for CCSP, despite encouraging preliminary results [3]. On the other hand, CCSP comes with drawbacks: variable R0 resection rates (32-96%) and up to 17.3% incomplete resection rates (IRR) [4-6], highlighting the need for improvement in cold snare resection techniques.

Underwater cold snare polypectomy (UCSP) was inspired by underwater endoscopic mucosal resection (UEMR) [7]. The

safety and efficacy of UEMR (with use of electrocautery) for the excision of larger polyps has already been reported in recent studies [8-10], yet data regarding UCSP for polyps <10 mm are insufficient. One of the advantages of underwater techniques is that water has a higher refractive index than air, and thus causes optical zoom of the mucosa. As a result, the mucosal architecture is more easily visible and the identification of polyp margins is facilitated, reducing residual lesions and recurrence risk. As lesions are more protuberant in a water-dilated than in an air-dilated colon, the endoscopist is able to snare a larger mucosal surface, increasing the chance of size-independent R0 resection [11-14]. However, UCSP is not usually performed outside specialized centers.

Interestingly enough, limited studies have assessed UCSP in clinical practice, reporting higher R0 resection rates (R0RR) and ratio of area containing the *muscularis mucosa* compared to CCSP [15-16]. However, these findings stem from studies that lacked sample power evaluation and featured a high proportion of polyps <8 mm in size. Maruoka *et al* first reported that the ratio of area containing *muscularis mucosa* was significantly higher in the UCSP group (UCSP: 50%, CCSP: 35.3%) indicating a broader resection. However, these data do not result from a randomized controlled trial. We present the first randomized controlled trial comparing UCSP with CCSP in terms of comprehensive histopathological evaluation, safety and efficacy, for resecting non-pedunculated colorectal polyps ranging from 5-10 mm in size.

Patients and methods

Study design

The COLDWATER study is a prospective, randomized, parallel, single-blind, controlled trial with allocation ratio 1:1 (referring to patients), aiming to compare underwater to conventional cold snare polypectomy for non-pedunculated colon polyps of size 5-10 mm. The study protocol has been published in a peer-reviewed journal indexed in MEDLINE [17]. The study design conforms to ICH–GCP (International Conference on Harmonization–Good Clinical Practice), and the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the "Sismanogleio" General Hospital of Athens (PN25771) and by the Committee of Bioethics and Ethics of the Medical School (PN526). The protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) design [18]. The study was registered with Clinical Trials.gov (NCT 05,273,697). This manuscript was written in accordance with the Consolidated Standards of Reporting Trials 2010 Statement (CONSORT) (Supplementary Table 1) [19].

[a]Second Department of Propaedeutic Surgery, "Laikon" General Hospital, Medical School, National and Kapodistrian University of Athens (Maria Zachou, Panayiotis Karantanos, Efthimia Lalla, Georgios Mpetsios, Maria Panoutsakou, Roxana Stoica); [b]Department of Gastroenterology, "Sismanogleio" General Hospital, Athens (Maria Zachou, Nikolaos Nikiteas, Stilianos Kykalos); [c]Department of Pathology, "Sismanogleio" General Hospital, Athens (Martha Nifora, Christina Zoumpouli); [d]Department of Pathophysiology, "Laikon" General Hospital, Medical School, National and Kapodistrian University of Athens (Theodoros Androutsakos, Stavros Sougioultzis); [e]Pediatric Department, General Hospital of Pella–Hospital Unit of Edessa (Georgios Katsaras); [f]Department of Gastroenterology, "Evangelismos" General Hospital, Athens (Konstantinos Varytimiadis); [g]Department of Surgery, "Hippocratio" General Hospital, Athens (Dionisia Thermou); [h]Unit of Hybrid Interventional Endoscopy, Department of Gastroenterology, Mediterraneo Hospital, Athens (Georgios Mavrogenis); [i]Intensive Care Unit, Sotiria Thoracic Diseases Hospital, Athens (Evangelia Ntikoudi); [j]Department of Gastroenterology, University Hospital of Heraklion, University of Crete, Heraklion (Evangelos Kalaitzakis); Greece

Randomization

The randomization process was single-blind and was conducted at patient level, using the random numbers method of Microsoft Excel 2016. A research assistant, who did not participate in the clinical practice, allocated the patients with a 1:1 ratio to the underwater and cold snare groups. The Excel distribution table was not accessible to the endoscopists.

Blinding

This was a single-blind study. Patients were not aware of the polypectomy procedure they would receive. Endoscopists could not be blinded because of the nature of the intervention. However, pathologists were blinded regarding the resection technique followed for each polyp.

Study objectives

The primary outcome of this study was the difference in the *muscularis mucosa* resection ratio (%) between the 2 polypectomy techniques. The *muscularis mucosa* resection ratio was calculated as: length of *muscularis mucosa* of the lesion in mm/length of specimen in mm × 100%.

Secondary objectives were related to the investigation of the difference between the 2 groups as regards the following items: presence or absence of submucosa in the specimen and its depth (if present), R0RR, IRR, *en bloc* resection rate, adverse events rate, and recurrence rate. Finally, a subgroup analysis was performed for all variables of interest in relation to the endoscopist's experience.

Study population and polyps

Patients scheduled for colonoscopy at the Gastroenterology Department of the "Sismanogleio" General Hospital of Athens were prospectively screened for eligibility. Patients aged >20 years, diagnosed with non-pedunculated polyps (Paris classification Isp, Is, IIa, IIb) [20] of size 5-10 mm, without endoscopic evidence of malignant submucosal infiltration,

were enrolled. The endoscopic diagnosis of mucosal lesions was based on their macroscopic appearance, such as deepening, ulceration/ulcer, abnormal vessels and irregular surface; all ascertained by at least 2 endoscopists. The size of each lesion was determined during the endoscopy procedure, by comparing the lesion with the closed (2 mm) or open (7 mm) biopsy forceps and was confirmed before resection by comparing it with the open snare (10 mm). Patients receiving antiplatelet/anticoagulant treatment were included in the study only if their treatment had been modified according to ESGE guidelines [21]. In patients diagnosed with more than 1 eligible polyp, all were resected by the same method. All patients provided written consent to participate in the study, after being thoroughly informed about the procedure.

Exclusion criteria for this study were: age ≤20 years; a diagnosis of idiopathic inflammatory bowel disease or severe organ failure; inadequately treated coagulopathies; lesions located at sites of previous polypectomy; and use of electrocautery/electrocoagulation during colonoscopy.

Study interventions

Colonoscopy and instruments

Endoscopists performed all endoscopic procedures with high definition Fujinon series instruments (Fujinon Corp., Omiya, Japan), while the use of a cap and the performance of the procedure with air or water or CO_2 was left to their preference. For the excision, a 0.3-mm dedicated cold snare with 10-mm diameter was used in both groups. The polyp size was estimated by visual comparison with the opening width of biopsy forceps (Radial Jaw 4 standard capacity, Boston Scientific, Marlborough, Massachusetts, USA). In order to specify the experience level of the endoscopist who performed the polypectomy, endoscopists were categorized as non-experts if they had conducted fewer than 1000 colonoscopies and 100 CCSPs.

USCP

Five steps were followed regarding the UCSP: a) complete air suction from the intestinal tract; b) partial opening of the intestinal lumen, using sterile water at room temperature through a water pump; c) immersion of the polyp in water; d) snaring of the polyp and 1-2 mm of the surrounding healthy tissue; and e) excision (Fig. 1).

CCSP

The CCSP technique followed 4 steps: a) aspiration of water, if water assisted colonoscopy was performed; b) insufflation of the intestinal lumen with air/CO_2); c) snaring of the polyp and 1-2 mm of the surrounding healthy tissue; and d) excision. The tissue specimens were placed in Vial 1.

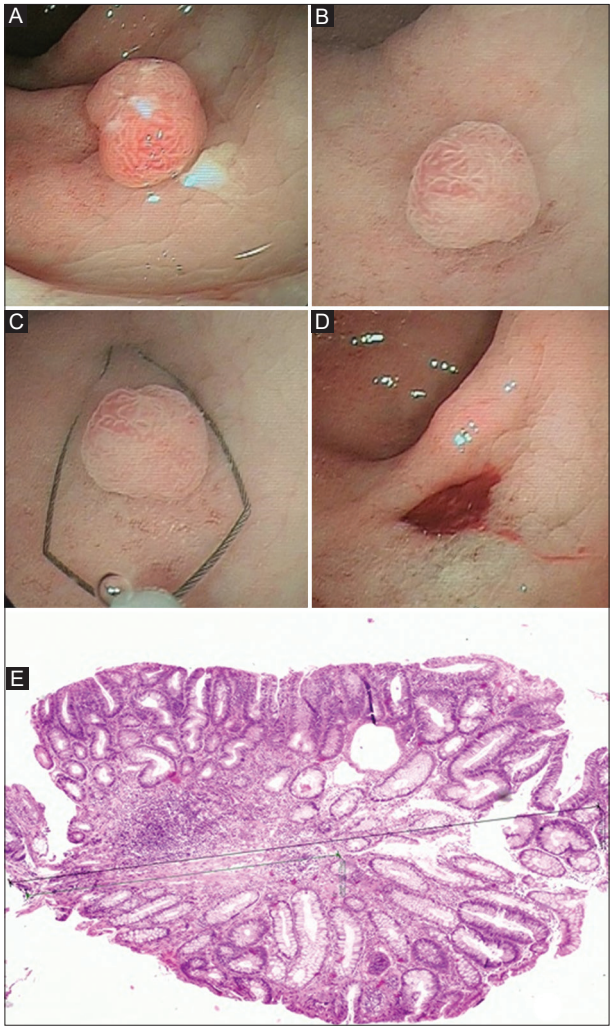

Figure 1 (A) A 5 mm Paris Isp low grade dysplasia tubular adenoma in a gas distended colon. (B) Lesion fully immersed in water (underwater). (C) snaring of the polyp underwater. (D) the defect at the polypectomy site after excision. (E) Part of a R0 resected tubular adenoma. The green line indicates the length of *muscularis mucosa* in this segment of the specimen and the black line indicates the total length of this part of the specimen

Resection point overview

After resection of the polyp, a thorough overview of the resection points for bleeding or perforation followed. Bleeding that persisted for >60 sec was characterized according to the ESGE guidelines [2] as intraprocedural bleeding, and treated either by water sprinkling or by placing hemostatic clips. At the end of the procedure, the resection site was reviewed endoscopically to confirm the completeness of the procedure.

Biopsies from resection site

In order to determine the IRR for polyps classified as Rx at pathological examination (according to the Residual Tumor Classification system [22]), additional biopsies were taken

from the resection site. To determine the horizontal margins, 2-4 biopsies were taken from the resection area (2 diametrically biopsies in polyps 5-7 mm, 4 biopsies in polyps 8-10 mm). The retrieved tissue was placed in Vial 1A.

Marking of lesion position

To easily locate the point of the polypectomy at follow-up colonoscopy, a submucosal tattoo was made 2-3 cm distal to each lesion. For rectal or cecal polyps, a submucosal tattoo was not required, and the positioning was aided by photographic recording prior to polypectomy.

Pathological examination

Specimens were placed in 2 vials with 10% formalin and were sent to the pathology laboratory. The slides were stained in the DAKO Cover Stainer using the DAKO Hematoxylin & Eosin Staining Kit, and were then evaluated by 2 independent experienced pathologists, under a Nikon Eclipse 50i and a Nikon Eclipse E400 optical microscope (4X). A Nikon 10X microscope lens was used for microscopic measurement. Dysplastic changes were classified using the Vienna classification system [22]. In the case of multiple tissue fragments, the parameters were calculated cumulatively.

Pathologists examining samples from Vial 1 performed: a) determination of the polypectomy margin according to Residual Tumor Classification [23], in order to report R0RR and IRR; b) calculation of the percentage of *muscularis mucosa* included in the specimen, according to the formula [length of *muscularis mucosa* of the lesion in mm/length of specimen in mm × 100%], after measuring the length and maximum depth of the *muscularis mucosa* underlying a neoplastic lesion, along with the specimen's maximum diameter, using an ocular and stage micrometer; c) determination of presence or absence of submucosa; and d) measurement of submucosa depth in μm when present. Pathologists examining samples from Vial 1A determined the horizontal margins in order to detect the presence or not of residual damage.

Follow up for adverse events

The study physician from the gastroenterology department evaluated any potential adverse events 30 days post-polypectomy through phone consultation.

Followup endoscopy

After 12 months, a follow-up endoscopy was performed to check for any recurrence of the resected lesion.

Statistical analysis

We estimated that to find a mean difference of 15% in the main outcome of the study (ratio of area containing *muscularis mucosa*, %) and based on the literature [15], 198 polyps were required per group (total 396) to find differences at a level of significance of 0.05. The enrolment stopped when we reached this goal. Absolute and relative frequencies, 95% confidence intervals (CI), and frequency graphs were used to illustrate the qualitative variables of the study. Mean values, standard deviations, median values and interquartile ranges were used to describe the quantitative variables. The Kolmogorov-Smirnov test was run to check the normality of the distributions. Pearson's chi-square and Fisher's exact test were applied to compare the ratios between the study groups. Student's t-test or the non-parametric Mann-Whitney test was used to compare quantitative variables between the 2 groups, depending on whether the data follow the normal distribution. In addition, linear or logarithmic models were used to check for differences between groups, taking into account other factors (e.g., resection technique, polyp size, location and histology, endoscopist's experience). A subgroup analysis was performed, after classifying endoscopists according their experience. to evaluate variations in both primary and secondary outcomes. Significance levels were bilateral and the threshold of statistical significance was set at 0.05. The analysis was run using the statistical program SPSS 26.0.

Results

Participants

From March 2021 to December 2022, we enrolled 229 patients with 408 colorectal lesions (intention-to-treat population) and randomly assigned them to the UCSP group (n=115 patients, n=203 polyps) or to the CCSP group (n=114 patients, n=205 polyps). In the UCSP group 2 polyps (0.96%) were not removed by UCSP, as it was not possible to immerse them in water, and thus were excluded. In addition, in the UCSP and CCSP groups 3 and 6 polyps, respectively, were not amenable to excision using a 10-mm diameter cold snare, necessitating a switch to a 15-mm diameter cold snare. These particular polyps were all 10 mm and Paris IIa and they were all excluded from the per-protocol analysis. A total of 220 patients with 397 colorectal lesions (115 patients and 198 polyps in the UCSP group; 114 patients and 199 polyps in the CCSP group) were finally included in the per-protocol analysis for the primary outcome (Fig. 2). Regarding the follow-up endoscopy 12 months after polypectomy, 63 patients in the UCSP and 74 patients in the CCSP group refused to participate because of anxiety about the hospital transmission of COVID 2019.

Endoscopic procedures and equipment

Altogether, 3 expert and 2 non-expert operators participated in this study. The same high-definition Fujinon video-colonoscope, equipped with water jet function, was used in each patient of the COLDWATER study. All procedures were performed without the use of a cap.

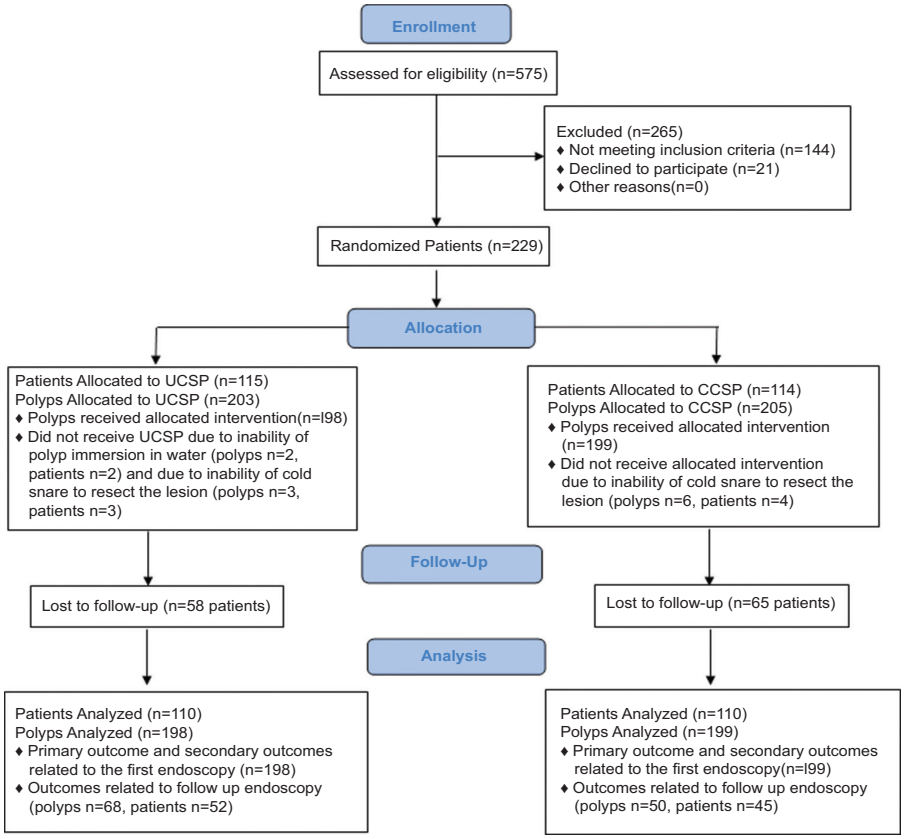

Figure 2 CONSORT 2010 flow diagram of the COLDWATER study
UCSP, Underwater cold snare polypectomy group; CCSP, conventional cold snare polypectomy group

Baseline data

Baseline characteristics of the patients, lesions and procedures are shown in Table 1. Altogether, 19 patients in the UCSP group and 20 patients in the CCSP group were on antithrombotic treatment. Both treatment groups were identical and homogeneous regarding the use of antithrombotic medication, polyp characteristics (location, size, histology and Paris classification) as well as the endoscopist's experience. Operator experience (non-expert vs. expert) was similar in the UCSP and CCSP groups (P=0.334).

Primary outcome

Primary and secondary outcomes are presented in Table 2. Regarding the primary outcome, *muscularis mucosa* resection ratio, UCSP was found to have better results compared to CCSP (P=0.003). Multiple linear regression analysis showed a statistically significant relationship between the ratio of area containing *muscularis mucosa* and the technique applied (P=0.044), whereas no such relationship was found for polyp location, *en bloc* resection, Paris classification, size category or endoscopist's experience (Supplementary Table 2). Subgroup analysis showed no differences for either group in the *muscularis mucosa* resection ratio in relation to the endoscopist's experience (Table 3).

Table 1 Baseline characteristics of the patients (A), lesions and procedures (B)

A. Characteristics of the patients in the COLDWATER study

Characteristic	UCSP group (n=110)	CCSP group (n=110)	P-value
Sex, male/female	65/45	68/42	0.93*
Median age, years (range)	61 (36-85)	61 (42-85)	0.87#
Antithrombotic treatment, n (%)	19/110 (17.3)	20/110 (18.2)	0.92*
Antiplatelet	8/19 (42.1)	7/20 (35)	
Double antiplatelet	3/19 (15.8)	3/20 (15)	
Anticoagulant	8/19 (42.1)	10/20 (50)	
None	91/110 (82.7)	90/100 (81.8)	
Type of antithrombotic	7/19 (37)	5/20 (25)	0.98*
Acetylsalicylic acid	1/19 (5.3)	2/20 (10)	
Clopidogrel	3/19 (15.7)	3/20 (15)	
Acetylsalicylic acid + clopidogrel			
Apixaban	3/19 (15.7)	4/20 (20)	
Rivaroxaban	3/19(15.7)	3/20 (15)	
Dabigatran	1/19 (5.3)	2/20 (10)	
Warfarin	1/19 (5.3)	1/20 (5)	

*Fisher's exact test (chi-square); #Mann-Whitney U

UCSP, underwater cold snare polypectomy; CCSP, conventional cold snare polypectomy

B. Characteristics of the polyps in the COLDWATER study

Characteristic	UCSP group (n=198)	CCSP group (n=199)	P-value
Location, n (%)			0.163*
Cecum	30 (15.2)	26 (13)	
Ascending	35 (17.8)	53 (26.7)	
Transverse	37 (18.7)	27 (13.6)	
escending	41 (20.7)	33 (16.6)	
Sigmoid	33 (16.5)	42 (21.1)	
Rectum	22 (11.1)	18 (9)	
Morphology - Paris Classification, n (%)			0.38*
Isp	78 (39.4)	66 (33.2)	
Is	83 (42)	90 (45.2)	
II-a	26 (13.1)	35 (17.6)	
II-b	11 (5.5)	8 (4)	
Median polyp size, mm (range)	7 (5-10)	6 (5-10)	0.87#
Mean SD polyp size, mm	6.95 1.52	6.72 1.56	0.87#
Size, mm			0.86#
5	39 (19.7)	56 (28.1)	
6	48 (24.2)	50 (25.1)	
7	47 (23.7)	34 (17.1)	
8	30 (15.2)	26 (13.1)	
9	16 (6.6)	19 (9.5)	
10	18 (10.6)	14 (7.1)	
Size category, mm			
5-7	134 (67.7)	140 (70.1)	0.58*
8-10	65 (32.2)	59 (29.9)	
Histological type, n (%)			
Tubular adenoma	101 (51)	108 (54.3)	0.31*
Villous adenoma	5 (2.5)	8 (4)	
Tubulovillous adenoma	63 (31.8)	48 (24.1)	
Sessile serrated adenoma	29 (14.7)	35 (17.6)	
Endoscopist, n (polypectomies)			
Non-expert	59	130	0.33*
Expert	139	69	

*Fisher's exact test (chi-square); #Mann-Whitney U

UCSP, underwater cold snare polypectomy; CCSP, conventional cold snare polypectomy

Table 2 Procedure-related outcomes. Primary and secondary outcomes of the COLDWATER study

Variables	UCSP (n=198)	CCSP (n=199)	P-value
Primary outcome			
Ratio of area containing *muscularis mucosa*, %			0.003#
Mean ± SD	81.72 ± 62.81	72.33 ± 22.33	
Median (IQR)	83.97 (35.71)	76.41 (29.41)	
Secondary Outcomes			
R0 resection, n (%)			
R0	186 (93.93)	179 (89.95)	0.29*
R1	2 (1.01)	5 (2.51)	
Rx	10 (5.05)	15 (7.54)	
Incomplete resection, n (%)	7 (3.5)	17 (8.5)	0.04*
En bloc resection, n (%)	194 (98)	186 (93.5)	0.04*
Containing SM tissue, n (%)	33 (16.6)	25 (12.5)	0.25*
Thickness of SM tissue, μm	76.5 (10.3)	73.6 (11.2)	0.3#
Mean (SD)			
Adverse event			
Bleeding, n (%)	1 (0.5)	4 (2)	0.37*
Recurrence, n (%)	2 (2.94)	1 (2)	0.75*
N refers to polypectomy sites	(n=68)	(n=50)	

*Fisher's exact test (chi-square), #Mann-Whitney U non-parametric test for 2 independent samples

UCSP, underwater cold snare polypectomy; CCSP, conventional cold snare polypectomy; SD, standard deviation; SM, submucosa

Secondary outcomes

Histology and endoscopy assessment

The submucosa was present in 12.5% in the UCSP group and 16% in the CCSP group (P=0.25). Although the R0RR was higher in the UCSP group than in the CCSP group (93.93% vs. 89.95%), this difference was not statistically significant (P=0.29). However, the IRR in the UCSP group was significantly lower than that in the CCSP group: 3.5% vs. 8.5% (P=0.05). Additionally, *en bloc* resections were achieved more frequently in the UCSP group than in the CCSP group (98% vs. 93.5%, P=0.04). Logistic regression analysis shows that R0RR had a significant positive association with *en bloc* resection (odds ratio [OR] 9.466, 95%CI 2.595-34.525; P=0.001), a negative association with location in sigmoid colon (OR 0.158, 95%CI 0.026-0.967; P=0.046), and a positive association with size category (5-7 mm; OR 4.62, 95%CI 1.87-11.415; P=0.001). In addition, e*n bloc* resection rate was significantly negatively associated with CCSP technique (OR 0.224, 95%CI 0.064-0.783; P=0.019), but positively associated with Paris Isp (OR 7.613, 95%CI 1.309-44.262; P=0.024) and size category 5-7 mm (OR 7.969, 95%CI 2.340-27.136; P=0.001), whereas the presence of submucosa in the specimen was not associated with any independent variable (Supplementary Table 2). Subgroup analysis revealed that in the CCSP group expert endoscopists achieved higher a R0RR than non-experts, while UCSP showed no significant R0RR difference across endoscopist's experience levels (Table 3).

Adverse events

Intraprocedural bleeding was the only observed adverse event (5 cases); in all cases it was easily controlled with use of a single hemostatic clip. The incidence of this adverse event did not differ between the 2 groups (UCSP 1/198, CCSP 4/199, P=0.37). In 2/5 cases the patient was regularly treated with antithrombotic agents (apixaban) and had modified treatment prior to endoscopy, according to ESGE guidelines. Regarding polyp size, 3/5 polyps were 7 mm and 2/5 were 8 mm, all Paris Isp. No patient was hospitalized after the intervention.

Follow-up endoscopy

Fifty-two patients (68 polyps) in the UCSP group and 45 patients (50 polyps) in the CCSP group underwent a follow-up endoscopy 12 months after the polypectomy. Polyp recurrence was observed in 3 cases (UCSP: 2.94%, CCSP: 2%, P=0.75). The initial lesions in 2 of the 3 cases of recurrence were of size 10 mm, while the other was of size 9 mm; all were tubular adenomas with high-grade dysplasia and R1 excision.

Discussion

To our knowledge, this is the first randomized controlled trial comparing UCSP and CCSP for small colorectal polyps,

Table 3 Subgroup analysis according to endoscopist's experience

Variable	Polypectomy by expert	Polypectomy by non-expert	P-value
Muscularis mucosa resection, Mean ± SD			
UCSP	81.5±38.4	86.5±31.5	0.1#
CCSP	76.3±32.6	76.4±27.5	0.7#
R0 Resection, n (%)			
UCSP	131/139 (94.2)	55/59 (93.2)	0.7*
CCSP	121/130 (93)	58/69 (84)	0.04*
Incomplete resection, n (%)			
UCSP	4/139 (2.9)	3/59 (5.1)	0.44*
CCSP	8/130 (6.2)	9/69 (13.1)	0.09*
En bloc resection, n (%)			
UCSP	136/139 (97.8)	58/59 (98.3)	0.99*
CCSP	122/130 (93.8)	64/69 (92.7)	0.7*
Containing SM tissue, n (%)			
UCSP	26/139 (18.7)	7/59 (11.9)	0.24*
CCSP	18/130 (13.8)	9/69 (13.1)	0.87*
Thickness of SM tissue, μm			
Mean (SD)			
UCSP	82±12.5	75.1±9.4	0.36#
CCSP	75.8±13.9	72.5±9.9	0.97#
Adverse events			
Bleeding, n (%)			
UCSP	1/139 (0.7)	0/59 (0)	0.12*
CCSP	2/130 (1.5)	2/69 (2.9)	0.5*

*Fisher's exact test

#Mann-Whitney U, 2 independent samples non-parametric test

SD, standard deviation; SM, submucosa; UCSP, underwater cold snare polypectomy; CCSP, conventional cold snare polypectomy

focusing particularly on the histologic characteristics of resection. In the COLDWATER study, UCSP was associated with a significantly higher ratio of *muscularis mucosa* resection, thus enabling a broader resection. Although there were no differences between the 2 treatment groups in terms of R0RR and submucosa excision, the UCSP group exhibited a higher *en bloc* resection rate and a lower IRR compared to the CCSP group.

CCSP stands as the established technique for removing small colorectal polyps [2]. Nevertheless, there is an ongoing debate regarding the predictability of *muscularis mucosa* resection. Previously published studies observed that *muscularis mucosa* was absent in 27.8% of excision specimens, while its presence ranged from 57-92%, even in cases involving cold snare polypectomy with submucosal injection [24-27]. The COLDWATER study revealed a significantly higher *muscularis mucosa* resection rate for UCSP (UCSP: 81.72±62.81%, CCSP: 72.33± 22.33%, P=0.003), suggesting a more favorable efficacy profile. This aligns with findings from a study by Maruoka *et al*, who initially assessed the efficacy of UCSP [16]. Furthermore, the UCSP technique emerged as an independent factor favoring extended *muscularis mucosa* excision, potentially contributing to achieving R0 resection, as demonstrated previously [25,28]. Interestingly, Maruoka *et al* [15] and Myung *et al* [16] reported a significantly higher R0RR in the UCSP group, which contrasts with the findings of the COLDWATER study, where no difference was observed between UCSP and CCSP. Our study revealed superiority of UCSP over CCSP concerning IRR, diverging from the results presented by Yen *et al* [29].

The presence of submucosa has been observed in 9-24% of resected specimens following CCSP [24,26,30]. However, our study revealed a superficial depth of excision, with only 16.6% and 12.5% of specimens including submucosa in UCSP and CCSP (P=0.25), respectively. The limited depth of resection and the inability to access and remove a portion of the submucosa are well-documented drawbacks of the cold snare technique [31,32], which, as per our findings, were not mitigated by the underwater technique. This suggests that, in adenomas with high-grade dysplasia, potentially concealing *in situ* or invasive cancer, both UCSP and CCSP are inferior to techniques involving electrocautery. Moreover, it appears that deeper resections are facilitated by the use of electrocautery and are not influenced by submucosal injection or water immersion in EMR or UCSP/UEMR, respectively.

Our results regarding the safety of UCSP align with the literature. Previous studies reported no clinically significant adverse event in either group [15,16,29]. As per the COLDWATER study findings, UCSP emerges as an exceptionally safe technique, with the sole adverse event being intra-procedural bleeding (UCSP: 0.5%, CCSP: 2%, P=0.37), effectively managed through mechanical hemostasis. The UCSP safety profile hinges primarily on employing a cold snare instead of electrocautery, and secondarily on using a water-distended colon rather than gas distention.

Perhaps the most noteworthy finding of the COLDWATER study is the favorable R0RR of UCSP, irrespective of the endoscopist's experience. While both UCSP and CCSP exhibit a high R0RR, only in UCSP does this appear to be unrelated to the endoscopist's experience, enabling both experts and non-experts to achieve adequate outcomes. This pivotal discovery from our study not only holds promise for young endoscopists striving for complete excision, but also for introducing polypectomy training in gastroenterology residents. UCSP ensures patient safety by minimizing the risk of incomplete resection. Considering that the removal of small polyps is a fundamental skill for every endoscopist, and that small polyps are the most prevalent during screening colonoscopes, perhaps local and international educational organizations should contemplate recommending the underwater technique for less experienced endoscopists

During the COLDWATER study, we observed certain issues associated with cold snare excision that fell beyond the scope of this research, yet remained noteworthy. Approximately 2.2% of enrolled polyps did not undergo the allocated intervention because of the cold snare's inability to excise the lesion. In these cases, we attempted to maneuver the snared polyp toward the endoscope tip and persisted with the snare closed, yet we were unable to successfully excise the polyp. Ultimately, we needed to switch to a 15-mm diameter snare to resect the polyp. These cases were deemed inappropriate for inclusion in the per-protocol analysis. Our conclusion, drawn from clinical experience, highlighted a potential correlation between polyp size, morphology, and snare diameter. All polyps measured 10 mm, exhibited Paris IIa morphology, and were initially subjected to a 10-mm snare. Further prospective randomized studies are necessary to comprehensively address this issue.

The COLDWATER study, despite yielding valuable insights, has certain limitations. Primarily, it was a single-center study involving multiple participating endoscopists. To mitigate potential bias, we opted to present comprehensive data concerning the endoscopists' experience and conducted a subgroup analysis, categorizing the endoscopists into experts and non-experts. This division was made according to the opinion of the research team and heterogeneous literature data [6,8,9,33]. Additionally, only 3 experts and 2 non-experts participated, and thus it is difficult to generalize the results. Secondly, blinding the endoscopists was not feasible; however, both pathologists and patients were blinded to ensure an objective assessment. Thirdly, the resection specimens were not pinned to a cork and thus the direction of sectioning did not ensure appropriate evaluation of the *muscularis mucosa* in a proportion of specimens. Lastly, an omission in our documentation includes the timing of procedures. Our experience suggested that UCSP generally required more time compared to CCSP, particularly in cases located in the sigmoid colon. However, we did not record specific time-related data. Contrarily, existing data from another randomized controlled trial support the inverse claim, indicating that resection time was longer in CCSP compared to UCSP for small polyps [16]. Future studies may be expected to provide detailed insights in this regard.Αρχή φόρμας

In summary, UCSP achieves a broader excision compared to CCSP concerning the *muscularis mucosa* resection ratio, despite not achieving a deeper excision. Moreover, UCSP demonstrates a higher rate of *en bloc* resections, a lower IRR, while it appears to be a promising technique for polypectomy

training among inexperienced endoscopists, given its experience-independent R0RR.

Summary Box

What is already known:

- Underwater cold snare polypectomy (UCSP) for small non-pedunculated colorectal polyps is a safe technique
- UCSP achieves a more extensive excision of the *muscularis mucosa* compared to conventional cold snare polypectomy (CCSP) according to the finding of a non-randomized controlled trial
- UCSP achieves a higher R0 resection rate compared to CCSP

What the new findings are:

- This is the first randomized controlled trial confirming that UCSP results in a higher *muscularis mucosa* resection rate than CCSP
- UCSP demonstrated a favorable R0 resection rate (R0RR) irrespective of the endoscopist's experience
- UCSP showed a higher *en bloc* resection rate and lower rates of incomplete resection than CCSP
- UCSP achieved a superficial depth of resection, indicated by the limited ability to access and remove a portion of the submucosa

References

1. de Benito Sanz M, Hernández L, Garcia Martinez MI, et al; POLIPEC HOT-COLD Study Group. Efficacy and safety of cold versus hot snare polypectomy for small (5-9mm) colorectal polyps: a multicenter randomized controlled trial. *Endoscopy* 2022;**54**:35-44.
2. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2017;**49**:270-297.
3. Thoguluva Chandrasekar V, Spadaccini M, Aziz M, et al. Cold snare endoscopic resection of nonpedunculated colorectal polyps larger than 10 mm: a systematic review and pooled-analysis. *Gastrointest Endosc* 2019;**89**:929-936.
4. Liu W, Gong J, Gu L. The efficacy and safety of cold snare versus hot snare polypectomy for endoscopic removal of small colorectal polyps: a systematic review and meta-analysis of randomized controlled trials. *Int J Colorectal Dis* 2023;**38**:136.
5. Maruoka D, Arai M, Akizue N, et al. Residual adenoma after cold snare polypectomy for small colorectal adenomas: a prospective clinical study. *Endoscopy* 2018;**50**:693-700.
6. Djinbachian R, Iratni R, Durand M, Marques P, von Renteln D. Rates of incomplete resection of 1- to 20-mm colorectal polyps: a systematic review and meta-analysis. *Gastroenterology* 2020;**159**:904-914.
7. Binmoeller KF, Weilert F, Shah J, Bhat Y, Kane S. "Underwater" EMR without submucosal injection for large sessile colorectal polyps (with video). *Gastrointest Endosc* 2012;**75**:1086-1091.
8. Yamashina T, Uedo N, Akasaka T, et al. Comparison of underwater vs conventional endoscopic mucosal resection of intermediate-size colorectal polyps. *Gastroenterology* 2019;**157**:451-461.
9. Nagl S, Ebigbo A, Goelder SK, et al. Underwater vs conventional endoscopic mucosal resection of large sessile or flat colorectal polyps: a prospective randomized controlled trial. *Gastroenterology* 2021;**161**:1460-1474.
10. Sundaram S, Seth V, Jearth V, Giri S. Underwater versus conventional endoscopic mucosal resection for sessile colorectal polyps: an updated systematic review and meta-analysis. *Rev Esp Enferm Dig* 2023;**115**:225-233.
11. Binmoeller KF. Underwater EMR without submucosal injection: is less more? *Gastrointest Endosc* 2019;**89**:1117-1119.
12. Cammarota G, Cesaro P, Cazzato A, et al. The water immersion technique is easy to learn for routine use during EGD for duodenal villous evaluation: a single-center 2-year experience. *J Clin Gastroenterol* 2009;**43**:244-248.
13. Binmoeller KF, Hamerski CM, Shah JN, Bhat YM, Kane SD, Garcia-Kennedy R. Attempted underwater *en bloc* resection for large (2-4 cm) colorectal laterally spreading tumors (with video). *Gastrointest Endosc* 2015;**81**:713-718.
14. Curcio G, Granata A, Ligresti D, et al. Underwater colorectal EMR: remodeling endoscopic mucosal resection. *Gastrointest Endosc* 2015;**81**:1238-1242.
15. Maruoka D, Kishimoto T, Matsumura T, et al. Underwater cold snare polypectomy for colorectal adenomas. *Dig Endosc* 2019;**31**:662-671.
16. Myung YS, Kwon H, Han J, et al. Underwater versus conventional cold snare polypectomy of colorectal polyps 4-9 mm in diameter: a prospective randomized controlled trial. *Surg Endosc* 2022;**36**:6527-6534.
17. Zachou M, Varytimiadis K, Androutsakos T, et al. Protocol design for randomized clinical trial to compare underwater cold snare polypectomy to conventional cold snare polypectomy for non-pedunculated colon polyps of size 5-10 mm (COLDWATER study). *Tech Coloproctol* 2023;**27**:325-333.
18. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;**5**:200-2007.
19. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med* 2010;**8**:18.
20. Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy* 2005;**37**:570-578.
21. Veitch AM, Radaelli F, Alikhan R, et al. Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline update. *Gut* 2021;**70**:1611-1628.
22. Rubio CA, Nesi G, Messerini L, et al. The Vienna classification applied to colorectal adenomas. *J Gastroenterol Hepatol* 2006;**21**:1697-1703.
23. Hermanek P, Wittekind C. Residual tumor (R) classification and prognosis. *Semin Surg Oncol* 1994;**10**:12-20.
24. Toyosawa J, Yamasaki Y, Fujimoto T, et al. Resection depth for small colorectal polyps comparing cold snare polypectomy, hot snare polypectomy and underwater endoscopic mucosal resection. *Endosc Int Open* 2022;**10**:E602-E608.
25. Shimodate Y, Itakura J, Mizuno M, et al. Factors associated with possibly inappropriate histological evaluation of excised specimens in cold-snare polypectomy for small colorectal polyps. *J Gastrointestin Liver Dis* 2018;**27**:25-30.
26. Suzuki S, Gotoda T, Kusano C, et al. Width and depth of resection for small colorectal polyps: hot versus cold snare polypectomy. *Gastrointest Endosc* 2018;**87**:1095-1103.
27. Shimodate Y, Itakura J, Takayama H, et al. Impact of submucosal

saline solution injection for cold snare polypectomy of small colorectal polyps: a randomized controlled study. *Gastrointest Endosc* 2020;**92**:715-722.
28. Hirose R, Yoshida N, Murakami T, et al. Histopathological analysis of cold snare polypectomy and its indication for colorectal polyps 10-14 mm in diameter. *Dig Endosc* 2017;**29**:594-601.
29. Yen AW, Leung JW, Wilson MD, Leung FW. Underwater versus conventional endoscopic resection of nondiminutive nonpedunculated colorectal lesions: a prospective randomized controlled trial (with video). *Gastrointest Endosc* 2020;**91**:643-654.
30. Ito A, Suga T, Ota H, Tateiwa N, Matsumoto A, Tanaka E. Resection depth and layer of cold snare polypectomy versus endoscopic mucosal resection. *J Gastroenterol* 2018;**53**:1171-1178.
31. Tutticci NJ, Kheir AO, Hewett DG. The cold revolution: how far can it go? *Gastrointest Endosc Clin N Am* 2019;**29**:721-736.
32. Shichijo S, Takeuchi Y, Kitamura M, et al. Does cold snare polypectomy completely resect the mucosal layer? A prospective single-center observational trial. *J Gastroenterol Hepatol* 2020;**35**:241-248.
33. Zhang Q, Gao P, Han B, Xu J, Shen Y. Polypectomy for complete endoscopic resection of small colorectal polyps. *Gastrointest Endosc* 2018;**87**:733-740.

Supplementary material

Supplementary Table 1 CONSORT 2010 checklist of information to include when reporting a randomized trial*

Section/Topic	Item No	Checklist item	Reported on page No
		Title and abstract	
	1a	Identification as a randomised trial in the title	3
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	N/A
		Introduction	
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	4
		Methods	
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3-4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	4-5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
		Randomization:	
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomization; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
		Results	
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	8
	13b	For each group, losses and exclusions after randomization, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow up	8
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8

(*Contd...*)

Supplementary Table 1 (*Continued*)

Section/Topic	Item No	Checklist item	Reported on page No
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8-9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
		Discussion	
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-11
		Other information	
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org

Supplementary Table 2 Results of multivariate analysis

Independent variables	Ratio of area containing *muscularis mucosa**	R0^	*En bloc*^	Presence of submucosa^
Technique	0.044	0.655 (0.273-1.572), 0.343	0.224 (0.064-0.783), 0.019	0.720 (0.358-1.450), 0.358
Location (Reference: rectum)	0.116			
Sigmoid		0.158 (0.026-0.967, 0.046	-	0.467 (0.114-1.912), 0.290
Descending		0.693 (0.177-2.709), 0.598	-	1.170 (0.356-3.847), 0.796
Transverse		0.274 (0.056-1.337), 0.110	-	1.240 (0.336-4.205), 0.729
Ascending		0.224 (0.050-1.014), 0.052	-	1.065 (0.329-3.449), 0.917
Cecum		0.409 (0.087-1.920), 0.257	-	0.140 (0.015-1.276), 0.081
En bloc (Reference: piecemeal)	0.823	9.466 (2.595-34.525), 0.001		
Paris (Reference: Paris Is)	0.753			
Isp		1.186 (0.420-3.348), 0.747	1,176 (0.309-4.479), 0.812	0.780 (0.357-1.702), 0.532
Is		1.945 (0.582-6.504), 0.280	0.535 (0.083-3.425), 0.509	0.693 (0.224-2.149), 0.526
IIa		1.926 (0.340-10.899), 0.458	7.613 (1.309-44.262), 0.024	1.082 (0.261-4.489), 0.913
Size category	0.112	4.62 (1.87-11.415), 0.001	7.969 (2.340-27.136), 0.001	1.119 (0.517-2.423), 0.776
Endoscopist's Experience	0.136	0.469 (0.202-1.085), 0.077	0.701 (0.226-2.170), 0.701	0.981 (0.474-2.029), 0.958
Ratio of area containing *muscularis mucosae*				0.986 (0.972-1.000), 0.055
R0 resection rate				1.906 (0.664-5.472), 0.230

*Multiple linear regression analysis. P-values are shown.

^Logistic regression analysis. Odds ratios (95% confidence intervals) and P-values are shown