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Incomplete resection rates of 4- to 20-mm non-pedunculated colorectal polyps when using wide-field cold snare resection with routine submucosal injection

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ABSTRACT

Background and study aims Incomplete resection of 4- to 20-mm colorectal polyps occur frequently (>10%), putting patients at risk for post-colonoscopy colorectal cancer. We hypothesized that routine use of wide-field cold snare resection with submucosal injection (CSP-SI) might reduce incomplete resection rates (IRRs).

Patients and methods Patients aged 45 to 80 years undergoing elective colonoscopies were enrolled in a prospective clinical study. All 4- to 20-mm non-pedunculated polyps were resected using CSP-SI. Post-polypectomy margin biopsies were obtained to determine IRRs through histopathology assessment. The primary outcome was IRR, defined as remnant polyp tissue found on margin biopsies. Secondary outcomes included technical success and complication rates.

Results A total of 429 patients (median age 65 years, 47.1% female, adenoma detection rate 40%) with 204 non-pedunculated colorectal polyps 4 to 20 mm removed using CSP-SI were included in the final analysis. CSP-SI was technical successful in 97.5% (199/204) of cases (5 conversion to hot snare polypectomy). IRR for CSP-SI was 3.8% (7/183) (95% confidence interval [CI] 2.7%-5.5%). IRR was 1.6% (2/129), 16% (4/25), and 3.4% (1/29) for adenomas, serrated lesions, and hyperplastic polyps respectively. IRR was 2.3% (2/87), 6.3% (4/64), 4.0% (6/151), and 3.1% (1/32) for polyps 4 to 5 mm, 6 to 9 mm, <10 mm, and 10 to 20 mm, respectively. There were no CSP-SI-related serious adverse events.

Conclusions Use of CSP-SI results in lower IRRs compared to what has previously been reported in the literature for hot or cold snare polypectomy when not using wide-field cold snare resection with submucosal injection. CSP-SI showed an excellent safety and efficacy profile, however comparative studies to CSP without SI are required to confirm these results.

Introduction

Colorectal cancer (CRC) is the third most incident cancer (10 %), and the second cause of cancer-related deaths (9.4 %) worldwide [1]. Among detected CRC cases, 6 % to 7 % occur after colonoscopy as interval CRC representing a failure in the screening and surveillance program [2–4]. Missed lesions and incomplete resection of colorectal polyps are the main risk factors for the development of interval CRC [5–9]. Ensuring complete endoscopic polyp resection is therefore important to reduce incidence of CRC and its related morbidity and mortality [6, 10–12].

Recent guidelines from the US Multi Society Task Force (USMSTF) and European Society of Gastrointestinal Endoscopy (ESGE) suggest use of cold snare polypectomy (CSP) for 1- to 9-mm polyps [8, 13]. CSP with or without SI was suggested as a potential primary approach for 10- to 19-mm polyps in USMSTF guidelines and as an alternate approach in cases where there is high risk of deep mural injury in ESGE guidelines [8, 13]. A recent meta-analysis indicated that incomplete resection rates (IRRs) when using CSP is high but comparable to IRRs when using hot snare polypectomy (HSP) [14]. A previous study conducted by our research group showed that CSP without SI for 4- to 20-mm colorectal polyps resulted in 19 % IRR [15]. In contrast, another study showed that wide-field cold polypectomy with SI was associated with a much lower IRR (1.2 %) when used for resection of large (> 10 mm) serrated lesions (SLs) [16]. We therefore hypothesized that a technique combining wide-field CSP with routine submucosal injection (CSP-SI) might result in low IRRs for 4- to 20-mm non-pedunculated colorectal polyps.

Patients and methods

This study has been reported according to the guidelines for reporting non-randomized pilot and feasibility studies [17].

Study design and patients

We conducted a prospective multi-endoscopist single-center cohort study. Patients 45 to 80 years undergoing elective screening, surveillance, or diagnostic colonoscopy at the Montreal University Hospital Center (CHUM) from January to October 2021 were enrolled. Exclusion criteria were: known inflammatory bowel disease; hereditary CRC syndromes; poor general health (defined as American Society of Anesthesiologists [ASA] classification > 3); coagulopathy (defined as international normalized ratio ≥ 1.5 or platelets < 50); poor bowel preparation (defined as Boston Bowel Preparation Score < 6, or < 2 in any colonic segment); emergency colonoscopies or hospitalized patients and pregnancy. The study was approved by the Montreal University Research Center Institutional Review Board (CER 20.111) and registered at ClinicalTrials.gov (NCT04548947). All patients signed a written informed consent form for study participation.

Colonoscopy and polypectomy procedures

All patients underwent bowel cleansing using a standard regimen (split-dose polyethylene glycol) before the colonoscopy. Patient antithrombotic and anticoagulation therapy was managed according to the American Society of Gastrointestinal Endoscopy (ASGE) guidelines [18]. The quality of bowel cleansing was assessed by the endoscopist during the procedure according to the Boston Bowel Preparation Scale [19]. Colonoscopies were performed by five board-certified gastroenterologists using high-definition colonoscopes (Olympus 190 series; Olympus, Center Valley, Pennsylvania, United States of America). The size of all detected polyps was estimated using a catheter tip of a closed snare (approximately 2.5 mm). Polyps were characterized for morphology according to the Paris classification [20] and location within the colon (proximal colon from cecum to splenic flexure, and distal colon from descending colon to rectum).

All detected 4- to 20-mm non-pedunculated polyps were resected using submucosal injection (ORISE; Boston Scientific, Marlborough, Massachusetts, United States) followed by wide-field cold snare resection (Captivator cold, 10 mm; Boston Scientific) (▶ **Video 1**). Polyps that could not be removed using CSP-SI (Cold snare polypectomy with submucosal injection) were removed using a hot snare or another standard resection technique according to the endoscopist judgment. After polypectomy, all resection margins were visually inspected using white-light endoscopy and/or narrow-band imaging for detection of any polyp remnants. Any remaining tissue was removed using a cold snare until polyp removal was visibly complete and polypectomy field was extended by at least 3 mm to achieve wide-field resection. After complete resection of all visible polyp tissue, biopsies were taken according to original polyp size: two margin biopsies from opposite sides of the resection defect for 4- to 9-mm polyps, and four margin biopsies from the four quadrants for 10- to 20-mm polyps.

Post-colonoscopy follow-up procedure

Post-procedure complications were assessed in the endoscopy suite, and the recovery room until patient discharge. All patients were contacted by telephone 14 days after the colonos-

VIDEO

▶ **Video 1** Injection and cold snare polypectomy technique.

copy to assess for any adverse events (AEs) (delayed bleeding; abdominal pain; perforation).

Histopathology evaluation

Board-certified pathologists assessed polyps for histopathology (according to the 2019 World Health Organization guideline) [21], and classified them as hyperplastic polyps, adenomas (e. g., villous adenomas, tubulovillous adenomas, tubular adenomas), SLs, high-grade dysplasia or cancer. Margin biopsies were assessed separately to determine the presence or absence of any remnant polyp tissue, and thus confirm complete or incomplete resection.

Study aims

The primary aim was the IRR of 4- to 20-mm non-pedunculated colorectal polyps following CSP-SI. Incomplete resection was defined as any margin biopsy containing tissue remnant corresponding to the pathology of the resected polyp (e. g., adenoma remnants in the margin biopsies after resection of an adenoma). Other outcomes included IRR stratified by polyp size, histology, location, endoscopist experience; technical success rates (defined as visually complete resection using CSP-SI exclusively without conversion to HSP); Intraprocedure bleeding rate (IPB); complication rate including delayed bleeding, abdominal pain, perforation; en bloc resection rate; visual incomplete resection after the first polypectomy cut.

The technical success rate was calculated as the number of polyps successfully resected with CSP-SI divided by the total number of polyps resected, excluding protocol deviations involving initial polyp removal by a technique other than CSP-SI. The conversion rate was defined as the proportion of polyps resected using a method other than CSP-SI after initial attempt with CSP-SI. Easy resection was defined as complete dissection of the submucosal plane upon closing the snare for the first time. Difficult resection was defined as not being able to dissect and complete polypectomy upon initial closing of the snare or physical manipulation such as “guillotine” technique being required. IPB was defined as any bleeding that occurred during endoscopy at the polypectomy site. IPB was defined as mild if no endoscopic treatment was required, and significant if endoscopic hemostasis was required. Delayed bleeding was defined as any bleeding post-procedure that necessitated a hospitalization or emergency room visit. Endoscopists with a practice that includes doing routinely referred endoscopic mucosal resection (EMR) cases prior to the study participation were considered experienced and those with no routine EMR practice were considered not experienced.

All polyps that were not adenomas, hyperplastic polyps, or SLs (e. g., those that were hamartomas, lymphoid aggregates, inflammatory polyps, subepithelial lesion, mucosal prolapse) were not included in the IRR analysis. Adenoma detection rates, calculated as the proportion of examinations with adenomas on the total number of examinations, and IRR were calculated for each participating endoscopist.

Sample size and statistical analysis

A previous study conducted by our research group showed that CSP without SI for 4- to 20-mm colorectal polyps resulted in high IRR (24/128 = 19 %) (12.4 %-26.6 %) [15]. We considered a reduction to 8.5 % to these previous findings as clinically significant for demonstrating clinical superiority of CSP-SI. A one-proportion chi-squared test with a 0.05 two-sided significance level (80 % power) allows the detection of such a difference or more when polyp sample size is 168. We expected a polyp detection rate of 40 %, therefore a sample size of at least 420 patients was deemed necessary for the study. To adjust for any study dropouts (e. g., inadequate bowel preparation, withdrawal of consent), we increased the overall sample size and enrolled a total of 435 patients. The study was not powered to detect variation in IRRs between the five endoscopists.

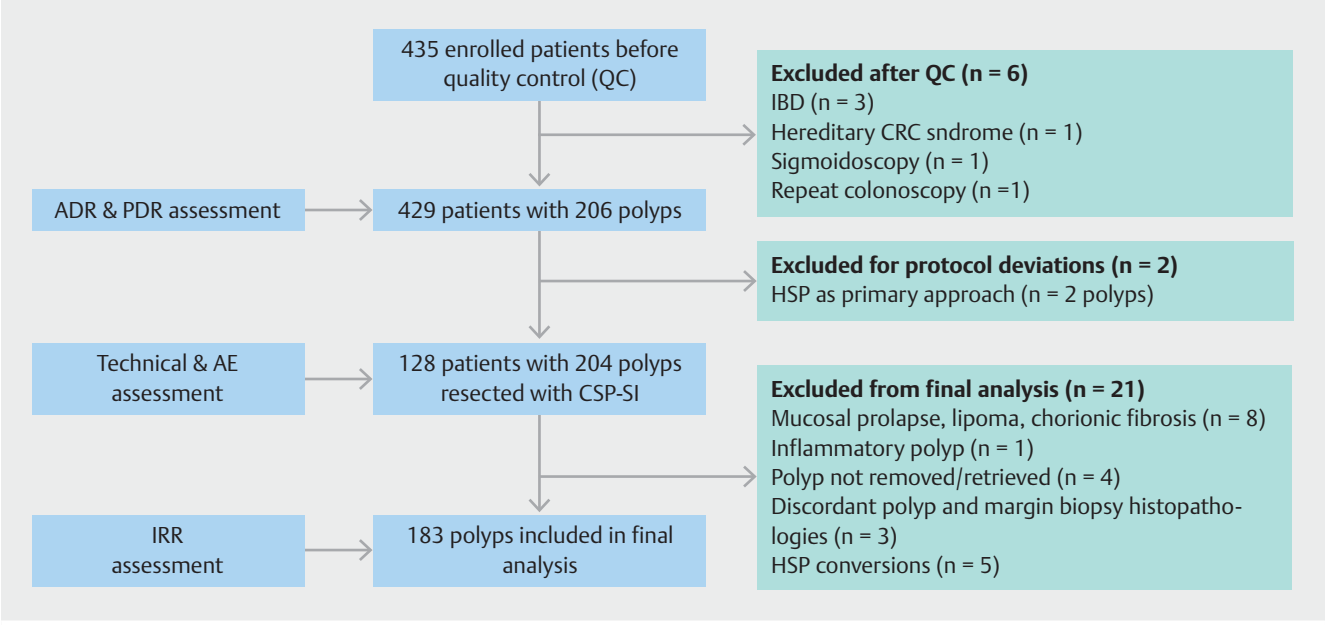
IRR was calculated as the number of polyps with positive margins determined by histopathological examination divided by the total number of polyps and is presented with 95 % confidence intervals (CIs). The IRR was calculated the 95 % CI considering the varying number of study polyps per patient, with a Bootstrap of 10 000 samples, stratified by patient record ID. Descriptive statistics are presented as numbers and frequencies for categorical variables, and as mean (standard deviation [SD]) or median (range) for continuous variables with normal and non-normal distribution, respectively.

To assess the predictors of incomplete resection, we used generalized estimating equations (GEEs) with logit link and exchangeable correlation matrix. The GEEs account for clustering of polyps within patients (as a patient may have more than one polyp). To construct the GEEs, we first conducted univariable logistic regression models and variables significant in these models at the $P<0.05$ were entered in the GEEs. The potential predictors considered included: polyp characteristics (i. e., size 4 to 5 mm vs. 6 to 9 mm vs. 10 to 20 mm), surface morphology (flat vs. non-flat), location (proximal vs. distal), histopathology (hyperplastic; SLs vs. adenomas (reference category); polypectomy characteristics such as polyp resection type (en bloc vs. piecemeal), ease of resection (easy vs. difficult); endoscopist-related characteristics (i. e. level of experience with CSP-SI (experienced with EMR vs. inexperienced with EMR), case volume, cecal intubation rate, and adenoma/polyp detection rate). Results were reported as odd ratios (ORs) with 95 % CIs. $P<0.05$ was considered statistically significant. Additional analyses were also performed to analyze the association between endoscopists (performing ≥ 14 polypectomies for 4- to 20-mm polyps) and incomplete resection, considering the endoscopist with the lowest IRR as reference. All statistical analyses were performed using SPSS statistics version 27 (IBM Corp., Armonk, New York, United States).

Results

Patient, procedure, and polyp characteristics

A total of 429 patients (median age 65 years; 47.1 % female) were enrolled in the study. After applying inclusion and exclusion criteria, a total of 429 patients were enrolled in the study,



▶ **Fig. 1** Patient enrollment flowchart.

of whom 128 patients with non-pedunculated polyps sized 4 to 20 mm were included in the final analyses (▶ **Fig. 1**). The included patients had 206 potentially eligible polyps and of these, 183 met the inclusion criteria and were included in the final analyses (▶ **Fig. 1**). Of the included polyps, 87 (47.5 %) were 4 to 5 mm, 64 (35.0 %) were 6 to 9 mm and 32 (17.5 %) were 10 to 20 mm. The majority of the polyps, 129 (70.5 %) were adenomas, 25 (13.6 %) SLs and 29 (15.8 %) HPs. Detailed patient, procedure, and polyp characteristics are provided in ▶ **Table 1**.

Technical outcomes and Incomplete resection rates

CSP-SI was reported to be technically easy in 92.6 % polypectomies (186/204). The rate of conversion to HSP was 2.5 % (5/204). Details of polypectomy procedure outcomes are shown in ▶ **Table 2**.

Of the 183 polyps included in the final analysis, seven were incompletely resected, with an overall IRR of 3.8 % (95 % CI 2.7–5.5 %). The GEE analyses revealed that the IRR was statistically significantly higher for SLs (16.0 %) (OR 12.11 [95 %CI 2.1–71.20]); and hyperplastic polyps (3.4 %) (OR 2.27 [0.19–28.02]) compared to adenomas (1.6 %) (P = 0.016). IRR for polyps 4 to 5 mm was 2.3 % vs 6.3 % for polyps 5 to 9 mm and 3.1 % for polyps 10 to 20 mm. IRR for polyps < 10 mm was 4.0 % (95 %CI 2.6–6.0). There was no statistically significant difference in IRR between the polyp size groups (P = 0.467) (▶ **Table 3**). IRR was higher for en bloc resection when compared to piecemeal resection although not statistically significant (5.8 vs 2.1 %; OR 2.9 [95 %CI 0.6–15.5]; P = 0.203). Difficulty in use of CSP-SI had statistically significantly higher IRRs compared with ease of use (18.2 vs 2.9 %) (OR 7.47 [95 %CI 1.28–43.75]; P = 0.026). Endoscopists inexperienced with EMR had statistically significantly higher IRRs compared to those who were experienced (10.5 vs 2.1 %; OR 5.75 [95 % CI 1.30–25.40]; P = 0.021). Endoscopists included in the study had varying results for endoscopic quality metrics, however, these did not seem to be associated with IRRs (▶ **Table 4**).

Adverse events

Mild self-limiting IPB occurred in 69 patients (53.9 %, 69/128) [95 % CI 44.87–62.75 %], four of which underwent clip placement (3.1 %, 4/128) [95 % CI 0.86–7.81 %]. During the 14-day post-intervention period, clinically significant delayed bleeding occurred in 0.8 % of patients (1/128) (95 % 0.02–4.28), abdominal pain in 17.2 % (22/128) (95 % CI 11.09–24.85), and no perforation occurred. Out of these events, clinically significant delayed bleeding related to CSP-SI occurred in no patients (0 %) and abdominal pain occurred in 7 % of patients (9/128) (95 % CI 3.27–12.93 %). No serious AEs were reported following polypectomy using the CSP-SI technique (▶ **Table 5**).

Discussion

In this prospective exploratory cohort study, we found that using CSP-SI was associated with low IRR (3.8 %). CSP has seen recent increased popularity due to its favorable safety profile, with current American and European guidelines in many cases recommending its use over HSP or cold forceps [8, 13]. There have been many studies evaluating IRRs for standard CSP with varying reported rates of 7 % to 30 % for varying polyp sizes [22–27]. A recent meta-analysis of IRRs found 17.3 % [95 % CI 14.3–20.3] IRR for CSP of 1- to 20-mm polyps which was similar to IRRs for HSP [14]. IRR therefore remains very high in the literature and could contribute to interval CRC cases, with studies attributing 20 % to 30 % of interval CRC to incomplete resection. Interval CRC is typically found in colon segments of previous polypectomy sites [28–33]. It is, therefore, important to reduce

▶ **Table 1** Patient, polyp and procedure characteristics.

Patients, n	**429**
Age, median (IQR) [range], years	65 (12) [45–80]
Sex, male, n (%)	227 (52.9)
ASA, n (%)	
▪ I	129 (30.1)
▪ II	277 (64.6)
▪ III	23 (5.4)
Anticoagulant and antiplatelet therapy, n (%)	93 (21.7)
▪ Antiplatelet	61 (14.2)
▪ Anticoagulant	32 (7.5)
Adenoma detection rate, n (%)	172 (40.1)
Adequate bowel preparation, n (%)	386 (90.0)
Polyps, n	183
Mean size [SD]	6.82 [3.5]
Location, n (%)	
▪ Proximal	121 (66.1)
▪ Distal	62 (33.9)
Paris classification	
▪ Is	139 (76.0)
▪ IIa	41 (22.4)
▪ IIc	3 (1.6)
Size	
▪ 4–5 mm, n (%)	87 (47.5)
▪ 6–9 mm, n (%)	64 (35.0)
▪ 10–20 mm, n (%)	32 (17.5)
Histology	
▪ Adenoma, n (%)	129 (70.5)
▪ Tubular adenomas, n (%)	120 (65.7)
▪ Villous adenomas, n (%)	1 (0.5)
▪ Tubulovillous adenomas, n (%)	6 (3.3)
▪ Tubulovillous adenomas with HGD, n (%)	2 (1.0)
▪ Sessile serrated lesions, n (%)	25 (13.7)
▪ Hyperplastic, n (%)	29 (15.8)

ASA, American Society of Anesthesiologists; IQR, interquartile range; HGD, high-grade dysplasia.

IRRs to ensure proper efficacy of CRC screening programs. In our study, SI and wide-field resection was used to counteract the high IRRs observed for standard CSP with significantly lower incomplete resection than the reported literature on standard CSP.

The use of EMR-style techniques for CSP of 4- to 20-mm polyps is very sparce in the literature with varying results. Two studies using normal saline SI found 5.9 % IRR when using cold EMR (C-EMR) in 6- to 20-mm polyps, and 7.2 % in 6- to 10-mm polyps [34, 35]. Another in 3- to 10-mm polyps found that SI did not improve the resection depth [36]. One study in 10- to 14-mm polyps using glycerol SI found excessively high (36.2 %) IRRs [37]. Gel injection solutions could offer more long-lasting dome-shaped cushion elevation underneath the mucosa compared to saline which is crucial for polypectomy [38]. In a previous randomized controlled trial (RCT), it was found that the use of a viscous gel injection reduced the resection times as well as the number of pieces significantly compared to NS [39]. Saline and HES are used as an off-label polypectomy aid, and they are time-consuming to prepare when MB or other agents are added in the solution. In our practice, we found pre-dyed gel injections quicker and easier to use compared to saline or HES. Although we did not measure injection times in all polypectomies, injection time was generally less than 1 minute and did not significantly impact procedure times rendering this option viable even for smaller polyps. Given the increased costs associated with utilization of gel-based SIs, head-to-head comparison to cheaper alternatives such as NS are required before widespread adoption.

A recent RCT compared cold snare, C-EMR, hot snare or hot EMR for resection of 6- to 15-mm non-pedunculated polyps. The study found that cold snare had the lowest IRR. However, the study was designed to demonstrate non-inferiority between the four different polypectomy techniques and thus included only 286 polypectomies randomized into the four groups and only seven incomplete resections were found across all four groups [40]. Furthermore, all polypectomies were performed by expert endoscopist with extensive EMR experience and polypectomy techniques were not standardized (i. e. different SI agents and different snare types were used within the same group). In contrast our study was comprised of a group of EMR experts and non-experts all using a standardized polypectomy technique. We found in our study that EMR experts tended to have lower IRR compared to non-experts. The use of wide-field EMR where the resection margins are systematically expanded might also have contributed to the results seen in our study when comparing the IRR found (3.8 %) compared to a much higher IRR found (19 %) in a previous study conducted by the same group of endoscopists using standard CSP alone and in comparison to hot snare study with similar methodology (▶ **Table 6**). However, further RCTs are required to demonstrate superiority regarding IRR between CSP, CSP-SI and hot snare-based techniques. It is possible that the wide-field resection aspects when using CSP would have also improved IRR. Indeed, recent publications have highlighted that wide-field resection allows for a better completion of the resection of lesions measuring less than 10 mm, and a lower IRR [41]. Furthermore, using the different technical approaches (e. g., SI versus no injection) needs to be evaluated for different polyp entities (i. e., SLs).

Polyp histology was indeed associated with IRR outcomes. SLs were found to have significantly higher IRR (16.0 %) when compared with adenomas (1.6 %) or hyperplastic polyps (3.4 %)

▶ **Table 2** Technical outcomes of CSP-SI.

	All polyps N = 204	4–5 mm	6–9 mm	10–20 mm	*P* value
Type of resection[1], n (%)					
▪ En bloc (n = 98)	98 (48)	60 (61.2)	34 (34.7)	4 (4.1)	< 0.001
▪ Piecemeal (n = 104)	104 (50.9)	37 (35.6)	35 (33.7)	32 (30.7)	
Ease of resection[2], n (%)					
▪ Easy (n = 186)	186 (91.2)	90 (48.4)	65 (34.9)	31 (16.7)	0.006
▪ Difficult (n = 11)	11 (5.4)	6 (54.5)	4 (36.4)	1 (9.1)	
Visible residual polyp after first cut					
▪ No (n = 124)	124 (60.8)	75 (0.8)	39 (31.5)	10 (8.1)	< 0.001
▪ Yes (n = 80)	80 (39.2)	22 (27.5)	32 (40)	26 (32.5)	

CSP-SI, cold snare resection with submucosal injection; HSP, hot snare polypectomy.
[1] Unknown resection technique for two polyps.
[2] Five HSP conversions and two non-resected polyps (N/A).

(OR 12.11, [95 % CI 2.10–71.20]; *P* = 0.016). This finding can be explained by SL's inconspicuous and usually indefinite border structure [42]. There is little data on CSP specifically for 1- to 20-mm SLs. One study in 10- to 20-mm polyps found 44.3 % IRR, however, recurrence rates were very low 4.9 %, in contrast to another study performed by expert endoscopists using SI where only 2 % were incompletely resected [43, 44]. Endoscopist expertise in conjunction with EMR-style techniques could therefore contribute toward reducing IRR. In our study, experienced endoscopists had statistically significantly lower IRR (2.1 vs 10.5 %) (OR 5.8 [95 %CI 1.30–25.40]) (*P* = 0.021), with a moderate IRR for SLs when compared to the literature when expert and non-expert endoscopists are combined (16.0 %).

Studies directly comparing CSP to HSP have shown increased IPB when using CSP; however, CSP had very low rates of delayed bleeding, which is a more significant outcome as it can be associated with significant morbidity compared to IPB which can be addressed during the procedure [35, 45–47]. One study directly comparing C-EMR to conventional EMR in > 20 mm polyps found no bleeding and no perforation in the C-EMR group compared with 5.1 % delayed bleeding and 0.6 % perforation in the EMR group [48]. We conducted systematic 14-day post-intervention period calls to all patients in the cohort. Furthermore, we conducted systematic assessment of IPB documenting non-significant self-limited bleeding. During the 14-day post-intervention period, clinically significant delayed bleeding related to CSP did not occur, highlighting the safety profile of this technique. Of the patients that experienced abdominal pain, two patients had non-study polyps cut with HSP.

Studies directly comparing CSP to HSP have shown increased IPB when using CSP; however, CSP had very low rates of delayed bleeding which is a more significant outcome as it can be associated with significant morbidity compared to IPB which can be addressed during the procedure [35, 46, 49–51]. There were no CSP-SI-related serious AEs (i. e., no perforations) in our study and no clinically significant delayed bleeding. CSP-SI is, therefore, very safe for 4- to 20-mm polyps. Some publications have reported histological changes caused by the gel injection utilized in our study, although our pathologists have not found any immediate changes in our large cohort pathology samples. The previously described findings were found in a cohort of less than 60 patients [52–54]. Therefore, a larger analysis would need to be conducted in comparison to another injection to associate these changes with the SI and follow-up will be planned in our cohort to assess these changes. Although a specific gel solution was used in our study, this does not preclude utilizing wide-field resection with SI with other solutions. Further studies are required to demonstrate generalizability using a wide range of injection solutions.

To our knowledge, very few studies reported on CSP-SI in 4- to 20-mm and no study reported on the use of gel submucosal injection substance. The granular reporting of polyp sizes and histology is a strength of our study. The inclusion of experienced and non-experienced endoscopist is an added strength and improves its generalizability to routine endoscopic practice. Our study, however, has several limitations such as the non-experienced endoscopists that contributed relatively fewer polypectomies to the study. The single-centered nature of the study could limit its generalizability and also larger RCTs are required. Any commercial injection solution such as the SI gel is certainly more expensive than a saline solution or HES although the latter are not US Food and Drug Administration-labeled for that use. Although we were able to observe a low IRR of 3.8 % with this injection, to confirm its beneficial use it would be important to pursue a comparative RCT study with saline in which the IRRs of non-pedunculated polyps sessile SLs are evaluated. Because our endoscopists resected 47 % of the lesions piecemeal, another limitation is the risk of local recurrence rate post-piecemeal resection. For the follow-up study, we plan a 2-year follow-up of this cohort to report if there were any recurrences for the seven IRRs (3.8 %) reported in this study. During that follow-up, we will also observe and report

▶ **Table 3** Incomplete resection rates after CSP-SI of colorectal polyps and associated predictors

	IRR, n (%)	Univariable OR [95 % CI]	*P* value
All (n = 183)	7 (3.8)		
Size, n (%)			
▪ 4–5 mm (n = 87)	2 (2.3)	1.00	0.467
▪ 6–9 mm (n = 64)	4 (6.3)	2.07 [0.22–19.3]	
▪ 10–20 mm (n = 32)	1 (3.1)	0.72 [0.06–8.33]	
Histology, n (%)			
▪ Adenoma (n = 129)	2 (1.6)	1.00	**0.016**
▪ Sessile serrated lesion (n = 25)	4 (16.0)	12.09 [2.08–70.24]	
▪ Hyperplastic (n = 29)	1 (3.4)	5.33 [0.55–51.27]	
Location, n (%)			
▪ Distal (n = 121)	5 (4.1)	1.00	0.761
▪ Proximal (n = 62)	2 (3.2)	1.29 [0.24–6.87]	
Type of resection, n (%)			
▪ Piecemeal (n = 97)	2 (2.1)	1.00	0.203
▪ En bloc (n = 86)	5 (5.8)	2.9 [0.55–15.52]	
Ease of resection, n (%)			
▪ Easy (n = 172)	5 (2.9)	1.00	**0.026**
▪ Difficult (n = 11)	2 (18.2)	7.42 [1.26–43.65]	
Visible residual polyp after first cut			
▪ No (n = 107)	5 (4.7)	1.00	0.484
▪ Yes (n = 76)	2 (2.6)	0.55 [0.10–2.92]	
Level of endoscopist experience			
▪ Experienced (n = 145)	3 (2.1)	1.00	**0.021**
▪ Not experienced (n = 38)	4 (10.5)	5.57 [1.19–26.05]	

CSP-SI, cold snare resection with submucosal injection; IRR, incomplete resection rate; OR: odds ratio.

▶ **Table 4** Endoscopist variability according to ADR, CIR and IRR (for 4– to 20-mm polyps).

Endoscopist	ADR (%)	CIR (%)	Withdrawal time median (IQR)	Study polyps removed (N = 206)	Average volume of submucosal gel injected per polyp (mL), median (IQR)	IRR (N = 183) n (%)
A	46.8	95.9	9 (6,14.25)	94	4 (2,5)	0 (0)
B	27.5	90.1	9 (7,14.25)	31	3 (2,6)	3 (11.5)
C	45	82.5	13 (9,23)	48	3 (2,4)	1 (2.3)
D	35.1	93.2	9 (6.5,15)	15	3 (2,7.5)	1 (8.3)
E	43.6	90.9	10 (8,15)	18	2 (1,4)	2 (12.5)
Group 1[1]	45	92.8	10 (7,16)	160	3 (2,5)	3 (2.1)
Group 2[2]	30.7	91.5	9 (7,15)	46	3 (2,6)	4 (11)

ADR, adenoma detection rate; CIR, cecal intubation rate; IRR, incomplete resection rate.
[1] Group 1, experienced endoscopists A, C & E.
[2] Group 2, non-experienced endoscopists B & D.

▶ **Table 5** Adverse outcomes related to CSP-SI.

	Patients N = 128	Confidence interval 95 % CI
Intraprocedure bleeding[1], n (%)		
None	46 (35.9)	27.65–44.89 %
Mild	69 (53.9)	44.87–62.75 %
Treatment needed	4 (3.1)	0.86–7.81 %
Delayed bleeding, n (%)	0 (0)	0.00–2.84 %
Abdominal pain, n (%)	9 (7)	3.27–12.93 %
Perforation, n (%)	0 (0)	0.00–2.84 %

CSP-SI, cold snare resection with submucosal injection; CI, confidence interval.
[1] Bleeding occurring during the procedure. Unknown bleeding for seven patients and not applicable to two patients; binomial Clopper-Pearson confidence interval.

any potential appearance of histological changes that were not observed in the present study.

Conclusions

In conclusion, CSP-SI results in very low (3.8 %) IRRs for 4- to 20-mm polyps. CSP-SI could be considered a safe and effective approach to remove 4- to 20-mm colorectal polyps; however, comparative studies of CSP without SI are required to confirm these results.

▶ **Table 6** Historical cold snare and hot snare polypectomy outcomes with or without submucosal injection.

	Cold snare with submucosal injection (CSP-SI study) N = 204	Cold snare without submucosal injection [15] (CSP study)[1] N = 182	Hot snare without submucosal injection [42] (CARE study)[2] N = 346
Polypectomy achieved as per protocol, n (%)	199 (97.5)	128 (70.3)	346 (100)
Ease of resection[3], n (%)			
▪ Easy	186 (90.3)	136 (77.7)	222 (64.2)
▪ Moderate	N/A	N/A	75 (21.7)
▪ Difficult	11 (5.3)	22 (12.6)	45 (13)
No (conversions)	5 (2.4)	17 (9.7)	0 (0)
Deviation	2 (1.0)	0 (0)	0 (0)
Volume of submucosal injection, median (IQR) mL	3.87 (2–5)	0 (0)	0 (0)
No. polyps included in the primary outcome analysis, n	183	128	346
Incomplete resection, n (%)	7 (3.8)	24 (19)	35 (10.1)
En bloc method, n (%)	86 (47)	128 (90.1)	286 (82.7)
Residual tissue after resection, n (%)	76 (41.5)	22 (15.4)	N/A
Bleeding[4], n (%)			
▪ None	85 (46.4)	65 (38.5)	261 (97)
▪ Mild IPB	85 (46.4)	96 (56.8)	N/A
▪ Treatment needed (any)	4 (2.2)	8 (4.7)	8 (3)

CSP-SI, cold snare resection with submucosal injection; CSP, cold snare polypectomy; IQR, interquartile range.
[1] Missing bleeding rate for 13 patients.
[2] Bleeding rate calculated on a total of patients (n = 269).
[3] Resection methods for two polyps are not applicable for CSP-SI study (N/A = 2).
[4] Unknown bleeding for seven patients and not applicable for two patients.

Competing interests

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Clinical trial

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References

[1] Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. American Cancer Society 2021; 71: 209–249

[2] Sanduleanu S, le Clerq CMC, Dekker E et al. Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. Gut 2015; 64: 1257–1267

[3] Samadder NJ, Curtin K, Tuohy TMF et al. Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. Gastroenterology 2014; 146: 950–960

[4] Cooper GS, Xu F, Barnholtz Sloan JS et al. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. Cancer 2012; 118: 3044–3052

[5] Pabby A, Schoen RE, Weissfeld JL et al. Analysis of colorectal cancer occurrence during surveillance colonoscopy in the dietary Polyp Prevention Trial. Gastrointest Endosc 2005; 61: 385–391

[6] Robertson D, Lieberman D, Winawer SJ et al. Interval cancer after total colonoscopy: results from a pooled analysis of eight studies. Gastroenterology 2008; 134: 111–112

[7] Pohl H, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. Clin Gastroenterol Hepatol 2010; 8: 858–864

[8] Ferlitsch M, Moss A, Hassan C et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Gastrointest Endosc 2017; 49: 270–297

[9] Kaminski MF, Regula J, Kraszewska E et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010; 362: 1795–1803

[10] Leung K, Pinsky P, Laiyemo AO et al. Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. Gastrointest Endosc 2010; 71: 111–117

[11] Farrar WD, Sawhney MS, Nelson DB et al. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol 2006; 4: 1259–1264

[12] Anderloni A, Jovani M, Hassan C et al. Advances, problems, and complications of polypectomy. Clin Exp Gastroenterol 2014; 7: 285–296

[13] Kaltenbach T, Anderson JC, Burke C et al. Endoscopic removal of colorectal lesionsd - recommendations by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc 2020; 91: 486–519

[14] Djinbachian R, Iratni R, Durand M et al. Rates of incomplete resection of 1- to 20-mm colorectal polyps: a systematic review and meta-analysis. Gastroenterology 2020; 159: 904–914 e912

[15] von Renteln D, Djinbachian R, Benard F et al. Incomplete resection of 4–20 mm colorectal polyps when using cold snare and associated factors. Endoscopy 2022: doi:10.1055/a-1978-3277

[16] Tuttici NJ, Hewett DG. Cold endoscopic mucosal resection of large sessile serrated polyps at colonoscopy (with video). Gastrointest Endosc 2017; 87: 837–842

[17] Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. Pilot Feasibility Stud 2019; 5: 114

[18] Acosta RD, Abraham NS. ASGE Standards of Practice Committee. et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc 2016; 83: 3–16

[19] Lai EJ, Calderwood AH. The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc 2009; 69: 620–625

[20] Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon. Gastrointest Endosc 2003; 58: S3–S43

[21] Nagtegaal ID, Odze RD, Klimstra D et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020; 76: 182–188

[22] Lee CK, Shim JJ, Jang JY. Cold snare polypectomy vs. cold forceps polypectomy using double-biopsy technique for removal of diminutive colorectal polyps: A prospective randomized study. Am J Gastroenterol 2013; 108: 1593–1600

[23] Horiuchi A, Hosoi K, Kajiyama M et al. Prospective, randomized comparison of 2 methods of cold snare polypectomy for small colorectal polyps. Gastrointest Endosc 2015; 82: 668–675

[24] Desai S, Gupta S, Copur-Dahi N et al. A prospective randomized study comparing jumbo biopsy forceps to cold snare for the resection of diminutive colorectal polyps. Surg Endosc 2019: doi:10.1007/s00464-019-06874-z

[25] Arimoto J, Chiba H, Ashikari K et al. Safety and efficacy of cold snare polypectomy for pedunculated (Ip) polyps measuring less than 10 mm in diameter. Int J Colorectal Dis 2020; 35: 859–867

[26] Djinbachian R, von Renteln D. Cold snare resection of colorectal polyps: updates and recent developments. Curr Treatment Options Gastroenterol 2022; 20: 221–237

[27] 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. Digest Endosc 2017; 29: 594–601

[28] Robertson DJ, Lieberman DA, Winawer SJ et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. Gut 2014; 63: 949–956

[29] Farrar WD, Sawhney MS, Nelson DB et al. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol 2006; 4: 1259–1264

[30] Tollivoro TA, Jensen CD, Marks AR et al. Index colonoscopy-related risk factors for postcolonoscopy colorectal cancers. Gastrointest Endosc 2019; 89: 168–176.e163

[31] Kim KO, Huh KC, Hong SP et al. Frequency and characteristics of interval colorectal cancer in actual clinical practice: a KASID multicenter study. Gut Liver 2018; 12: 537–543

[32] Samadder NJ, Curtin K, Tuohy TMF et al. Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. Gastroenterology 2014; 146: 950–960

[33] Adler J, Toy D, Anderson JC et al. Metachronous neoplasias arise in a higher proportion of colon segments from which large polyps were previously removed, and can be used to estimate incomplete resection of 10-20 mm colorectal polyps. Clin Gastroenterol Hepatol 2019; 11: 2277–2284

[34] Li D, Wang W, Xie J et al. Efficacy and safety of three different endoscopic methods in treatment of 6-20 mm colorectal polyps. Scand J Gastroenterol 2020; 55: 362–370

[35] Papastergiou V, Paraskeva KD, Fragaki M et al. Cold versus hot endoscopic mucosal resection for nonpedunculated colorectal polyps sized 6-10 mm: A randomized trial. Endoscopy 2018; 50: 403–411

[36] 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.e711

[37] Yabuuchi Y, Imai K, Hotta K et al. Efficacy and safety of cold-snare endoscopic mucosal resection for colorectal adenomas 10 to 14 mm in size: a prospective observational study. Gastrointest Endosc 2020; 92: 1239–1246

[38] Moss A, Bourke MJ, Metz AJ. A randomized, double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyps of the colon. American Journal of Gastroenterology 2010; 105: 2375–2382

[39] Repici A, Wallace M, Sharma P et al. A novel submucosal injection solution for endoscopic resection of large colorectal lesions: a randomized, double-blind trial. Gastrointest Endosc 2018; 88: 527–535.e525

[40] Rex D, Anderson J, Pohl H et al. Cold versus hot snare resection with or without submucosal injection of 6-15 mm colorectal polyps: a randomized controlled trial. Gastrointest Endosc 2022: doi:10.1016/j.gie.2022.03.006

[41] Sidhu M, Forbes N, Tate D et al. Randomized controlled trial of cold snare polypectomy technique: technique matters more than snare wire diameter. Am J Gastroenterol 2022; 117: 100

[42] Pohl H, Srivastava A, Bensen SP et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology 2013; 144: 74–80

[43] Tutticci NJ, Hewett DG. Cold EMR of large sessile serrated polyps at colonoscopy (with video). Gastrointest Endosc 2018; 87: 837–842

[44] Yoshida N, Inoue K, Tomita Y et al. Cold snare polypectomy for large sessile serrated lesions is safe but follow-up is needed: a single-centre retrospective study. United European Gastroenterol J 2021; 9: 370–377

[45] Yamashina T, Fukuhara M, Maruo T et al. Cold snare polypectomy reduced delayed postpolypectomy bleeding compared with conventional hot polypectomy: a propensity score-matching analysis. Endosc Int Open 2017; 05: E587–E594

[46] Kawamura T, Takeuchi Y, Asai S et al. A comparison of the resection rate for cold and hot snare polypectomy for 4-9 mm colorectal polyps: A multicentre randomised controlled trial (CRESCENT study). Gut 2018; 67: 1950–1957

[47] Ket SN, Mangira D, Ng A et al. Complications of cold versus hot snare polypectomy of 10-20 mm polyps: A retrospective cohort study. JGH Open 2019; 4: 172–177

[48] van Hattem WA, Shahidi N, Vosko S et al. Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods. Gut 2021; 70: 1691

[49] Yamashina T, Fukuhara M, Maruo T et al. Cold snare polypectomy reduced delayed postpolypectomy bleeding compared with conventional hot polypectomy: a propensity score-matching analysis. Endosc Int Open 2017; 5: E587–E594

[50] Ket S, Mangira D, Ng A et al. Complications of cold versus hot snare polypectomy of 10-20 mm polyps: A retrospective cohort study. JGH Open 2019; 4: 172–177

[51] Thoguluva Chandrasekar V, Aziz M, Patel H et al. Efficacy and safety of endoscopic resection of sessile serrated polyps 10 mm or larger: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2020; 18: 2448–2455

[52] Ibarra-Arzamendia PN, Hanly MG. Histopathological findings related to ORISE injectable submucosa lifting agent used in the endoscopic mucosal resection of bowel neoplasms: a review of three cases. Case Rep Pathol 2020; 2020: 6918093

[53] Olivas A, Setia N, Weber C et al. Histologic changes caused by orise gel injection in gastrointestinal specimens. Modern Pathology 2020; 33: 739–740

[54] Lahr R, DeWitt J, Zhang D et al. Assessment of submucosal distortion and mass effect seen at follow-up after colorectal EMR with ORISE (with video). Gastrointest Endosc 2022; 96: 679–668