Published online: 2021-08-23



# Cold snare polypectomy without submucosal injection: safety and efficacy in 615 large serrated lesions

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submitted 25.11.2020
accepted after revision 3.5.2021

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Endosc Int Open 2021; 09: E1421–E1426
DOI 10.1055/a-1517-4054
ISSN 2364-3722

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## ABSTRACT

**Background and study aim** Cold resection is becoming the standard of care for the resection of nonpedunculated colon lesions up to 10 mm in diameter. Sessile serrated adenomas/polyps (SSA/Ps), including those ≥ 10 mm, present various characteristics that make them ideal candidates for cold snare polypectomy (CSP).

**Patients and methods** A prospectively maintained database was searched retrospectively for consecutive patients with lesions ≥ 10 mm resected between March 2013 and March 2018. During that period, all SSA/P-appearing lesions were resected using CSP without submucosal injection, except for lesions with endoscopic suspicion of dysplasia or submucosal invasion. Patients with a pathological diagnosis of SSA/P were included in the analysis. Adverse events were recorded up to 21 days following colonoscopy.

**Results** 615 SSA/Ps ≥ 10 mm were resected during 452 colonoscopy procedures in 379 patients (mean age 54.1 years; standard deviation [SD] 11.9 years). Mean polyp size was 13.7 (SD 5.2) mm; 122 lesions (19.8 %) were ≥ 20 mm and 479 lesions (77.9 %) underwent piecemeal resection. Immediate adverse events included persistent abdominal pain that resolved spontaneously within 2 hours in three patients (0.8 %; 95 % confidence interval [CI] 0.2 %–2.3 %). One patient with persistent intraprocedural bleeding was successfully treated with a hemostatic clip. No late adverse events were detected. Surveillance colonoscopy was performed in 293 patients (77.3 %) at 23.4 (SD 11.6) months following index colonoscopy; residual/recurrent lesions were diagnosed in 23 patients (7.8 %; 95 %CI 5.0 %–11.6 %).

**Conclusion** CSP without submucosal injection appeared to be safe and effective for the resection of large SSA/Ps.

## Introduction

During the past 5 years, cold snare polypectomy (CSP) has become the predominant resection technique for 4–10 mm polyps [1]. Indeed, CSP has been recommended by the American Society for Gastrointestinal Endoscopy (ASGE) [2] and the European Society of Gastrointestinal Endoscopy [3] for the resection of nonpedunculated lesions < 10 mm in size, while the British Society of Gastroenterology has suggested its use for serrated lesions < 1 cm located in the proximal colon [4]. These recommendations were mostly based on the good safety profile of CSP but they have also recently been supported by efficacy studies showing similar rates of complete resection for cold vs. hot snare polypectomy [5,6]. Furthermore, the time and cost requirements of CSP are advantageous compared with those of hot snare polypectomy. These advantages would

make CSP the preferred technique, particularly for serrated lesions located in the proximal colon [4].

The serrated pathway of carcinogenesis accounts for 20 %–30 % of sporadic colorectal cancers (CRCs) [7, 8], and 5 %–7 % of interval CRCs [9, 10]. Among serrated lesions, sessile serrated adenomas/polyps (SSA/Ps) are the main precursors of CRCs and their resection is considered mandatory [11]. Large SSA/Ps are mostly located in the proximal colon and are usually flat; compared with conventional adenomas, they present a looser adherence to the submucosa, have a low incidence of dysplasia, and a lower risk of submucosal invasion and recurrence [11–13]. These unique characteristics make them ideal candidates for cold resection techniques.

Nevertheless, hot snare polypectomy is currently the gold standard for large (≥ 10 mm) SSA/Ps because the experience accumulated in the management of conventional adenomas has been transferred to these lesions. Most adverse events related to hot snare polypectomy, such as late bleeding, post-polypectomy syndrome, and perforation, are inherent to the use of electrocautery and are acceptable only if compared with the morbidity and mortality of surgery. We have described the use of CSP for large flat colorectal lesions [14, 15], and other authors have confirmed that CSP, preceded [16] or not [17] by submucosal injection, may be used to resect large SSA/Ps.

In this study, we evaluated the long-term safety and efficacy of CSP without submucosal injection for SSA/Ps ≥ 10 mm.

## Methods

We performed a retrospective review of a prospectively maintained database of colonic lesions resected at an outpatient endoscopy center between 1 March 2013 and 1 March 2018. During that period, all polyps with an endoscopic appearance suggestive of SSA/Ps were resected using the CSP technique without submucosal injection, except for lesions with endoscopic suspicion of dysplasia or of submucosal invasion (Kudo III-IV-V pit pattern, type 0-IIa with components 0-Is/0-IIc of the Paris classification) and ulcerated lesions (type 0-III of the Paris classification) [18]. Details of the patients, procedures, and endoscopic characteristics were prospectively recorded in the database. Written consent for the procedure was obtained from all patients. The study was approved by the local ethics committee.

Patients were included if they had at least one colonic lesion ≥ 10 mm resected with a diagnosis of SSA/P at pathological examination. There were no patients on anticoagulant and/or antiplatelet agents as no colonoscopic procedures are performed under these conditions in our ambulatory endoscopy center (patients taking aspirin for secondary prophylaxis are referred to a hospital, as we try to resect all polyps during the first screening colonoscopy procedure and the risk of bleeding is increased with large colonic endoscopic mucosal resection [EMR] if patients take aspirin) [19]. Surveillance colonoscopies were included up to 1 March 2020.

### Colonoscopy procedure

All procedures were performed by four endoscopists with experience in CSP of large nonpedunculated lesions using Olympus 150, H180, and H190 video colonoscopes (Olympus, Tokyo, Japan) under monitored anesthesia care. No caps were used and air was used for gut distension. Exacto snares (US Endoscopy, Mentor, Ohio, USA) were used for all resections; these snares are designed for cold resection and are made of a 0.3-mm braided wire with an opening diameter of 9 × 19 mm. A technique similar to that reported by other authors was used [20]. First, the lesion was measured using the deployed snare as a reference and, if the margins of the lesion were poorly defined, chromoendoscopy using 5 % acetic acid was used at the endoscopist's discretion [21]. No submucosal injection was performed. If possible, en bloc resection, including 2 mm or more of surrounding normal-looking tissue, was attempted. Briefly, the snare catheter was pressed onto the mucosa, the endoscope tip was angled towards the colonic wall, gentle aspiration was applied, and the snare was progressively closed until transection was achieved. For piecemeal resections, sections were repeated from one end of the lesion to the other end in a parallel fashion.

For lesions measuring between 10 and 19 mm, a technical variant was used to increase the likelihood of en bloc resection: the open snare was applied as for a piecemeal resection, closed almost up to the cutting point, completely reopened, and then the entire lesion was captured and resected. This approach is often effective as the adherence of SSA/Ps to the submucosa is loose. If transection was not possible due to the entrapment of excess tissue, the snare was slightly opened to free the trapped submucosa and the snare was then closed to achieve transection.

Following resection, the mucosal defect was flushed with water using a water pump in order to stretch the defect, shorten the bleeding time, and evaluate the edges for residual neoplastic tissue. The defect was observed for 60 seconds to detect possible persistent bleeding; if this occurred, hemostatic clips were applied. No hemostatic clips or cautery devices were used for prophylactic purposes. Evidence or suspicion of residual neoplastic tissue was treated by additional resection using a cold snare or a biopsy forceps. The specimens were recovered using forceps to prevent further tissue fragmentation, stretched onto a paper, placed in 4 % formaldehyde, and sent to the pathology laboratory.

Microscopic examination of resected specimens was performed by two expert pathologists and SSA/Ps were diagnosed using the World Health Organization (WHO) 2010 criteria [22].

Patients were discharged after anesthetic recovery with written instructions to contact the endoscopy center by phone or in person if they had pain, bleeding, or fever. Patients were also given an appointment at 3 weeks to receive the pathology report and for clinical evaluation.

## Patient surveillance method

Patients were asked to attend follow-up for endoscopic surveillance after 3 months to 3 years, depending on the size, number, and pathology of the polyps, resection technique (en bloc or piecemeal), and presence or absence of a serrated polyposis syndrome [4, 23].

At follow-up colonoscopy, assessment for residual or recurrent neoplastic tissue was conducted using a high-definition colonoscope with white-light and narrow-band imaging, complemented with acetic acid chromoendoscopy at the endoscopist's discretion. All detected neoplastic lesions were resected and sent for pathological examination.

## Definitions and end points

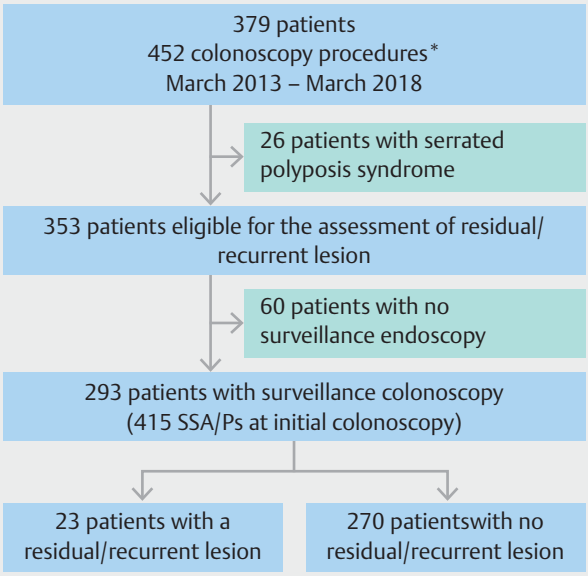
The primary end point was adverse events, including immediate and delayed bleeding or perforation, and pain, as well as deep mural injury defined according to the ASGE 2010 lexicon [24]; the secondary end point was local recurrence. End points were defined retrospectively. An immediate bleeding or perforation was defined as one that required treatment during the procedure, and late bleeding was defined as bleeding requiring medical treatment or emergency endoscopy during the 21 days following the procedure. Deep mural injury was defined as the visualization of the muscularis propria in the mucosal defect, and late perforation was defined as compatible clinical findings that required hospital admission and confirmation on computed tomography scan.

Immediate post-colonoscopy abdominal pain was not considered a clinically significant adverse event unless its intensity or duration required monitoring for longer than 1 hour.

A residual/recurrent lesion was defined as a lesion resected in an anatomical segment where an SSA/P had been resected during index colonoscopy and in which serrated tissue was detected at pathological examination. No attempt was made to distinguish a residual/recurrent lesion from missed or new SSA/Ps. The anatomic segments were cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum. The SSA/P recurrence rate was calculated per patient after exclusion of patients with a serrated polyposis syndrome defined according to WHO 2010 criteria [22].

## Statistical analysis

Patient and polyp characteristics, as well as adverse events, are described as percentages or mean (standard deviation [SD]) depending on whether they are categorical or continuous variables. The association between the finding of residual/recurrent lesions and patient characteristics (age at time of resection and sex) and polyp characteristics in each colon segment monitored for residual/recurrent lesion (location [proximal vs. distal], resection of a single vs. multiple SSA/Ps, size in mm) was investigated using Prism 9.0.1 for Mac (GraphPad, San Diego, California, USA). Comparisons between the groups were performed with the Pearson chi-squared test or Fisher's exact test for categorical data and the two-sample unpaired *t* test for continuous data; *P* values of $<0.05$ were considered statistically significant.




▶ **Fig. 1** Patients enrolled and performance of surveillance colonoscopy. *50 and 12 patients, respectively, had 2 and ≥3 colonoscopy procedures performed for the assessment of residual/recurrent lesions. SSA/Ps, sessile serrated adenomas/polyps.

# Results

A total of 615 SSA/Ps were resected by CSP during 452 colonoscopy procedures performed in 379 patients (▶ **Fig. 1**). The mean age was 54.1 (SD 11.9) years and 252 patients (66.5 %) were women (▶ **Table 1**). The mean lesion size was 13.7 (SD 5.2) mm (range 10–45 mm), 122 lesions (19.8 %) were ≥20 mm, and 18 (2.9 %) were ≥30 mm; 534 lesions (86.8 %) were located proximally to the splenic flexure. CSP was performed en bloc and piecemeal for 136 (22.1 %) and 479 (77.9 %) SSA/Ps, respectively. A total of 100 patients (26.4 %) had more than one synchronous SSA/P and 26 patients (6.9 %) had a previous diagnosis of serrated polyposis syndrome.

A total of 314 patients (82.8 %) attended the scheduled consultation 3 weeks after the procedure, and 65 patients (17.2 %) were contacted by phone to assess for adverse events, share the pathology results, and suggest an interval for follow-up colonoscopy. Thus, information for adverse events was available for 100 % of the patients.

## Adverse events

During recovery following colonoscopy, three patients (0.8 %; 95 % confidence interval [CI], 0.2 %–2.3 %) had persistent abdominal pain that resolved spontaneously within 2 hours (▶ **Table 2**). Pain was attributed to colonic distension by air. There was one case of persistent intraprocedural bleeding (0.3 %; 95 %CI 0–0.9 %): venous bleeding was noted from the protruding submucosa after resection of a 12-mm type 0-Is polyp; bleeding was stopped by applying a hemostatic clip and no other treatment was required. There was no evidence of deep mural injury

▶ **Table 1** Baseline characteristics of the 379 patients and 615 sessile serrated polyps.

| | |
|---|---|
| **Patients n** | |
| Female, n (%) | 252 (66.5) |
| Age, mean (SD), years | 54.1 (11.9) |
| **Lesions** | |
| Size | |
| ▪ Mean (SD), mm | 13.7 (5.2) |
| ▪ ≥20 mm, n (%) | 122 (19.8) |
| ▪ ≥30 mm, n (%) | 18 (2.9) |
| Location, n (%) | |
| ▪ Right colon | 343 (55.8) |
| ▪ Transverse including hepatic and splenic flexures | 191 (31.1) |
| ▪ Left colon | 81 (13.2) |
| Paris classification, n (%) | |
| ▪ 0-Is | 75 (12.2) |
| ▪ 0-Is | 3 (0.5) |
| ▪ 0-IIa | 528 (85.8) |
| ▪ 0-IIb | 9 (1.5) |
| Synchronous polypectomy, n | 267 |
| Dysplasia, n (%) | |
| ▪ Low grade | 19 (3.1) |
| ▪ High grade | 1 (0.2) |

SD, standard deviation.

in any patient. At 21 days, no bleeding, post-polypectomy syndrome, or late perforation were detected.

▶ **Table 2** Adverse events and residual/recurrent lesions.

| | |
|---|---|
| **Procedural adverse event** | |
| ▪ Patients, n | 379 (100) |
| ▪ Abdominal pain, n (%) [95 %CI] | 3 (0.8) [0.2–2.3] |
| Delayed adverse event, n | 0 |
| **Follow-up colonoscopy** | |
| ▪ Patients, n (%) | 293 (77.3) |
| ▪ Interval before first surveillance colonoscopy, mean (SD), months | 23.4 (11.6) |
| ▪ Residual/recurrent lesion detected, n (%) [95 %CI] | 23 (7.8) [5.0–11.6] |

CI, confidence interval; SD, standard deviation

## Surveillance

A total of 293 patients (77.3 %) underwent a follow-up colonoscopy for the assessment of residual/recurrent lesion over a period of 7 years (▶ **Fig. 1**). The mean follow-up interval was 23.4 (SD 11.6) months (range 3–71 months), with an interval for patients with an SSA/Ps ≥ 20 mm of 19.4 (SD 13.4) months (range 3–59 months). Overall, 24 residual/recurrent lesions were diagnosed in 23 patients (7.8 %; 95 %CI 5.0 %–11.6 %). The mean interval to surveillance colonoscopies that were positive for a residual/recurrent lesion was 26.2 (SD 15.8) months. The finding of residual/recurrent lesions was associated with the location of SSA/Ps in the proximal colon and a larger polyp size (▶ **Table 3**).

# Discussion

Based on the largest series to date, this study suggests that CSP without submucosal injection is safe and effective to remove large (≥ 10 mm) SSA/Ps. Our main finding was the absence of clinically significant adverse events in 615 resections performed en bloc or piecemeal. Three patients (0.8 %) experienced abdominal pain, and the only bleeding that was detected

▶ **Table 3** Association between the finding of residual/recurrent lesion at surveillance colonoscopy and the patient and polyp characteristics at index colonoscopy.

| | Residual/recurrent lesion | | *P* value |
|---|---|---|---|
| | Yes | No | |
| Patient characteristics (n = 293) | | | |
| ▪ Age, mean (SD), years | 55.8 (11.9) | 53.8 (11.8) | 0.43 |
| ▪ Male/female sex, n | 8/15 | 91/179 | 0.92 |
| Polyp characteristics in the 334 colon segments monitored for residual/recurrent lesions[1] | | | |
| ▪ Proximal/distal location, n | 24/0 | 260/50 | 0.03 |
| ▪ Single/multiple SSA/Ps, n | 18/6 | 260/50 | 0.39 |
| ▪ Size of the largest polyp, mean (SD), mm | 16.0 (7.4) | 13.7 (5.1) | 0.03 |

[1] 334 anatomic segments of the colon (in which 415 SSA/Ps had been resected at index colonoscopy) were monitored for residual/recurrent lesion at surveillance colonoscopy in 293 patients.

was immediate and was successfully treated with a hemostatic clip (immediate bleeding rate 0.3 %). No late bleedings, deep mural injury, or perforations were detected. This low adverse event rate compares favorably with that reported following hot snare polypectomy with submucosal injection (EMR), the current reference standard: in a series of 246 patients with SSA/Ps ≥ 20 mm, intraprocedural and late bleeding, deep mural injury, and perforation were reported in 6.9 %, 5.7 %, 2.8 %, and 0.4 %, respectively [12].

Other authors have also reported low rates of adverse events with cold snare resection for large polyps, with or without submucosal injection: 1.1 % in a meta-analysis (eight studies, of which five used submucosal injection, for a total of 522 colorectal adenomas and SSP/As ≥ 10 mm) [25], and 3.9 % of 205 patients with serrated lesions ≥ 10 mm resected by cold snaring with submucosal injection in a subsequent study (no intervention required for any adverse event) [26]. With respect to bowel perforation, only two cases have been reported following CSP and were probably due to inadequate technique (insufficient colonic distension) and the use of a snare not specifically designed for CSP [27]. Finally, a meta-analysis of three randomized trials concluded that immediate bleeding was less frequent with hot snare polypectomy than with cold snare polypectomy but endoscopic hemostasis was successful in all cases [6].

With respect to cold resection of large polyps, two strategies have been proposed, often named EMR or CSP depending on whether cold snaring is preceded or not by submucosal injection, respectively [14, 28]. Indeed, submucosal injection was proposed in 1955 to protect the deep colonic layers from thermal injury but this is not applicable to cold snaring [29]. We do not use submucosal injection because it involves additional time and cost and has no proven benefit. Furthermore, it may make tissue entrapment difficult and increases the surface area to be resected. Submucosal injection might be advantageous in difficult locations to better expose polyps, and it may also help to define polyp margins/detect residual tissue, but this may also be achieved with acetic acid chromoendoscopy. A randomized controlled trial would help to determine whether EMR or CSP is the best approach.

Polyp recurrence was detected in 7.8 % (95 %CI 5.0 %–11.6 %) of our patients after a mean of approximately 2 years. In the abovementioned meta-analysis [25], recurrence was reported for 2 (1.1 %) of 183 sessile serrated polyps during a follow-up period of 5.1–8.6 months. In the more recent series of cold EMR for serrated lesions [26], 18 residual lesions were found for 225 resected lesions (8.0 %; 95 %CI 5–12.1) in 110 patients who underwent a follow-up colonoscopy at a median of 12.4 months. This was similar to the series of 246 patients with SSA/Ps ≥ 20 mm treated by hot EMR, which reported a recurrence rate per patient of 7.0 % after a median of 13 months [12]. Of note, we defined SSA/P recurrence as any serrated tissue found at pathological examination in anatomical segments identical to the monitored lesions, with no attempt made to distinguish recurrence from missed or new lesions. This, together with the longer interval before the first colonoscopic surveillance compared with other studies has the potential to overestimate the rate of residual/recurrent SSA/Ps. Taken as a whole, these data support the guideline recommendation to perform endoscopic surveillance at 3 years following the resection of SSA/Ps ≥ 10 mm [4, 30].

The main limitation of our study is its retrospective design; the end points were retrospectively defined, no specific datasheet was used for data collection, and procedure reports were reviewed retrospectively. We attempted to mitigate the drawbacks inherent to retrospective studies by including consecutive individuals and by obtaining 3-week follow-up for all of them (we routinely ask for complications at this time). However, we acknowledge that non-severe complications, particularly pain, may have been missed due to the study design. The strengths of the study include a large sample size, the use of a standardized technique, and a long surveillance period. Randomized controlled trials are needed to compare the effectiveness of hot EMR vs. cold EMR vs. CSP in the resection of large SSA/Ps. We also propose that future randomized studies evaluate the application of CSP in large and flat conventional adenomas.

In conclusion, this study based on the largest series of cases to date showed that CSP applied to large SSA/Ps had good safety and efficacy profiles. This, added to the accessibility and low cost of CSP, suggests that CSP without submucosal injection may be the treatment of choice for large SSA/Ps.

## Competing interests

The authors declare that they have no conflict of interest.

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