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ENDOSCOPY

Cold Versus Hot Snare Endoscopic Resection of Large Nonpedunculated Colorectal Polyps: Randomized Controlled German CHRONICLE Trial

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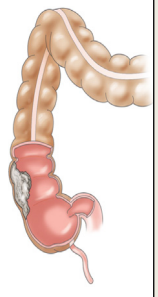
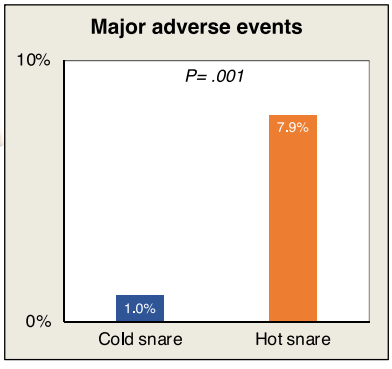
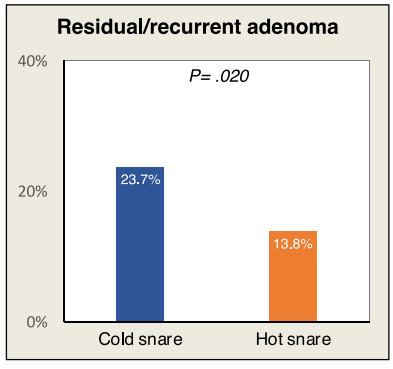
Cold versus Hot Snare Endoscopic Resection of Large Non-Pedunculated Colorectal Polyps (Randomized-controlled German CHRONICLE-trial)

Major adverse events are a relevant problem of hot snare-EMR of non-pedunculated colorectal polyps ≥ 2cm.







Cold snare-EMR appears safer than hot snare-EMR with an almost complete elimination of major adverse events, but results in a higher rate of residual adenoma at the first endoscopic follow-up.

Gastroenterology

BACKGROUND & AIMS: Endoscopic mucosal resection (EMR) is standard therapy for nonpedunculated colorectal polyps ≥20 mm. It has been suggested recently that polyp resection without current (cold resection) may be superior to the standard technique using cutting/coagulation current (hot resection) by reducing adverse events (AEs), but evidence from a randomized trial is missing. **METHODS:** In this randomized controlled multicentric trial involving 19 centers, nonpedunculated colorectal polyps ≥20 mm were randomly assigned to cold or hot EMR. The primary outcome was major AE (eg, perforation or postendoscopic bleeding). Among secondary outcomes, major AE subcategories, postpolypectomy syndrome, and residual adenoma were most relevant. **RESULTS:** Between 2021 and 2023, there were 396 polyps in 363 patients (48.2% were female) enrolled for the intention-to-treat analysis. Major AEs occurred in 1.0% of the cold group and in 7.9% of the hot group ($P = .001$; odds ratio [OR], 0.12; 95% CI, 0.03–0.54). Rates for perforation and postendoscopic bleeding were significantly lower in the cold group, with 0% vs 3.9% ($P = .007$) and 1.0% vs 4.4% ($P = .040$). Postpolypectomy syndrome occurred with similar frequency (3.1% vs 4.4%; $P = .490$). After cold resection, residual adenoma was found more frequently, with 23.7% vs 13.8% ($P = .020$; OR, 1.94; 95% CI, 1.12–3.38). In multivariable analysis, lesion diameter of ≥4 cm was an independent predictor both for major AEs (OR, 3.37) and residual adenoma (OR, 2.47) and high-grade dysplasia/cancer for residual adenoma (OR, 2.92). **CONCLUSIONS:** Cold resection of large, nonpedunculated colorectal polyps appears to be considerably safer than hot EMR; however, at the cost of a higher residual adenoma rate. Further studies have to confirm to what extent polyp size and histology can determine an individualized approach. German Clinical Trials Registry (Deutsches Register Klinischer Studien), Number DRKS00025170.

Keywords: Colonoscopy; Endoscopic Resection; Endoscopic Mucosal Resection; Cold Snare; Hot Snare; Adverse Event; Complication; Residual Adenoma.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Hot snare endoscopic mucosal resection (EMR) is the standard therapy for the resection of nonpedunculated polyps ≥2 cm, but major adverse events are a clinically relevant problem.

NEW FINDINGS

In this randomized controlled trial, cold snare EMR appeared to be safer than hot snare resection, with almost complete elimination of major adverse events, but resulted in a higher rate of residual neoplasia. However, in selected lesions, this drawback appears to be only minor.

LIMITATIONS

Real-life data with a certain variability of some technical issues, probable selection bias regarding localization and histology, use of some subjective morphology-based criteria, small number of main outcomes, and impossibility to blind the endoscopists to the group allocation were the limitations.

CLINICAL RESEARCH RELEVANCE

Cold snare EMR should be considered as a new therapeutic option for selected large colorectal polyps due to its superior safety profile. However, the exact definition of the ideal lesions requires further research.

BASIC RESEARCH RELEVANCE

Cold EMR needs some improvement regarding technical modifications of the snares and additional measures (eg, additional margin coagulation) to make it more effective.

Endoscopic mucosal resection (EMR) of adenomas during colonoscopy reduces colorectal cancer–related mortality.[1] Although smaller adenomas can be removed using several techniques, hot snare resection with combined cutting and coagulation current is considered standard of care for larger polyps. For lesions of ≥2 cm, this is mostly achieved in 2 or more pieces, called "piecemeal" EMR.[2]

In the past, rates of recurrent adenoma (more precisely residual/recurrent adenoma/neoplasia) after piecemeal EMR at follow-up (FU) endoscopy ranged from 15% to >40%.[3–7] In recent studies, reductions in recurrence rates to ≤5% were achieved with the use of additional margin coagulation,[8,9] or to <6.5% with underwater EMR.[10,11] However, hot piecemeal EMR is also associated with adverse events (AEs), such as perforation in 0.9%–2.7%,[12–14] relevant postprocedural bleeding in 6.2%–7.0%,[15–17] and postprocedural pain (postpolypectomy syndrome) in 5% of cases.[4] Recent studies have reported that with complete closure of the mucosal defect with clips, the rate of postendoscopic bleeding can be reduced to 3.5%.[18–20]

Another potentially easier and less costly option to reduce the rate of major AEs is cold snare resection, which is already established for smaller polyps. Here, reduced bleeding rates have been reported, even in patients receiving anticoagulant therapy.[21] For larger colorectal polyps, first results suggest a similar trend.[22] However, residual adenoma/recurrence may be observed more frequently, although this observation is based on uncontrolled, retrospective case series.[23,24]

For both outcome parameters, only evidence from randomized controlled trials (RCTs) can reliably help decide whether to use hot or cold snare resection for larger polyps. Therefore, we present the results of the first RCT comparing cold snare EMR of nonpedunculated polyps ≥20 mm with hot snare EMR in a multicentric setting (The German CHRONICLE [Cold vs Hot Snare Resection of Large Non-Pedunculated Polyps in the Colorectum] trial).

Abbreviations used in this paper: **AE, adverse event; ASGE, American Society of Gastroenterology; EMR, endoscopic mucosal resection; FU, follow-up; ITT, intention-to-treat; LST, laterally spreading tumor; OR, odds ratio; RCT, randomized controlled study; SSL, sessile serrated lesion.**

Most current article

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Materials and Methods

Study Design

We conducted an investigator-initiated, multicentric RCT with the participation of 19 tertiary referral centers in Germany. The study center was the Evangelische Diakoniekrankenhaus in Freiburg. The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki. It was approved by the responsible ethics committee of the University of Freiburg on April 15, 2021 and by the ethics committees of all participating hospitals. The study protocol was not changed after trial commencement and was registered with the German Clinical Trials Registry (Deutsches Register Klinischer Studien, Number DRKS00025170) before initiation. Data were collected prospectively at patient admission, during and after the procedure, and during FU examinations. This article was written according to the Consolidated Standards of Reporting Trials statement.[25]

Study Population and Polyps

All patients who were referred to the participating hospitals for resection of a large, colorectal polyp were screened for inclusion. Inclusion criteria were all colorectal nonpedunculated polyps ≥20 mm. Exclusion criteria are provided in Supplementary Table 1 and were, among others, pedunculated or residual/recurrent polyps; suspected or histologically confirmed malignancy; polyps with nodules too large (>1–1.5 cm) for use of a cold snare; or antiplatelet/anticoagulant medication that could not be paused as recommended in the current guideline.[26] More than 1 polyp per patient could be included if inclusion and exclusion criteria were fulfilled for each lesion. In these cases, major AEs should be traced back to the individual polyp via information from repeated colonoscopy and/or surgery and computed tomography.

A 1:1 randomization was performed by means of opening the opaque, sealed, and numbered envelopes in the endoscopy room after confirmed eligibility via endoscopic evaluation (details in Supplementary Table 2). All patients were blinded to the randomization result until the first FU. A blinding of the examiner was not possible. If a patient had more than 1 eligible lesion, a separate randomization was performed for each polyp in accordance with the randomization in previous related studies.[10,27]

Endoscopic Procedures and Follow-up

All colonoscopies were carried out according to guideline standards[2] after bowel preparation with the use of a high-definition video colonoscope, CO_2 insufflation, and propofol sedation. The resections were performed by endoscopists who had performed more than 1000 colonoscopies and had experience with hot and cold snare resections in at least 200 procedures. An examination of the potentially eligible polyp was performed by the endoscopist before randomization. Polyp size was measured by placing the open snare of defined size next to the lesion as a reference, in line with previous studies.[28] Macroscopic polyp morphology was evaluated according to the classifications of Paris and laterally spreading tumors (LSTs) or suspected sessile serrated lesions (SSL), as recommended.[2]

Depending on the randomization result, a dedicated cold (thin-wire) or hot snare or a hybrid snare (with/without current) was used for the resection. In the standard treatment group, the entire lesion was removed by means of hot snare resection according to guideline recommendations.[2,29] A detailed description of the different treatment options in both groups is provided in Supplementary Table 3 and successful cold and hot snare resections are shown in Figures 1 and 2. Normal saline was usually used as injectate, possibly with the addition of staining liquids (eg, indigo carmine or toloidine blue) and/or diluted adrenaline solution (1:10,000) according to the local routine. Beginning at the edge (with a small margin of surrounding normal tissue) snare resection usually had to be repeated several times for complete removal of the lesion (ie, the piecemeal technique). In both groups, use of prior and subsequent submucosal injections, clips, and snare exchange with no specifications in terms of company, type, or size was possible. If there were difficulties in cutting through tissue during cold snare EMR, repeatedly opening and closing of the snare, straightening of the catheter, or a jerky pull maneuver was performed to ensure a successful resection. Use of any hemostatic spray or gel was not allowed. In case of its use, conversion to a different resection modality, or use of diathermy-based techniques in the cold-snare group, the procedure was included in the intention-to-treat (ITT) analysis, but not in the per-protocol (PP) analysis. Treatment of AEs was not standardized and was carried out at the discretion of the attending physicians.

Histologic evaluation of the specimens was performed by expert gastrointestinal pathologists in every participating center according to the valid guidelines.[2,29]

After 4 weeks, a standardized telephone interview was conducted to inquire about postdischarge symptoms and/or AEs. If the interview did not take place, it was conducted during the first endoscopic FU, which occurred in 16 of 351 cases. The endoscopic FU was scheduled after 4 (±2) months, following the recommendations of the German guideline after piecemeal resection.[29] In case of residual/recurrent neoplasia, an endoscopic resection should be performed. The removal technique was at the discretion of the examiner. In case of an inconspicuous scar, biopsies should be taken. If surgery was required after initial resection, the surgical specimen was examined for residual/recurrent lesion at the former resection site.

Outcomes

All outcome parameters were assessed at the participating hospitals and later transmitted to the study center on paper case report forms that were not changed after trial commencement.

The primary outcome parameter was rate of major AEs as a combined end point, including any intra- or postprocedural perforation (ie, Sydney classification type 3–5[30]) or postendoscopic bleeding (ie, bleeding after completion of the procedure necessitating prolonged hospitalization; emergency department presentation; and/or endoscopic, angiographic, or surgical intervention).[17,28] Self-limited clinical bleeding that did not result in patient presentation for medical assessment or was managed by means of observation on an outpatient basis was not included in this category. Similarly, postpolypectomy syndrome was not included in this end point because it is not well-defined and was not counted as a major AE in a recent review of the American Society of Gastrointestinal Endoscopy (ASGE).[14]

Secondary outcomes were major AE subcategories (ie, perforation and postendoscopic bleeding), intraprocedural

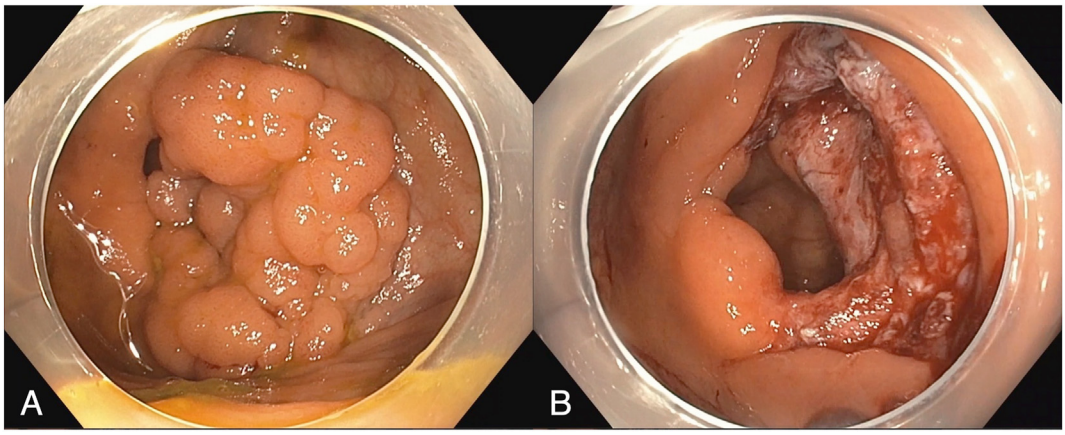

Figure 1. LST nodular-mixed type in the ascending colon before (*A*) and after (*B*) cold snare piecemeal EMR.

bleeding, postpolypectomy syndrome, technical success (ie, removal of the lesion without conversion), resection speed, and the rate of residual/recurrent adenoma/neoplasia at the first FU endoscopy (or in case of surgery in the surgical preparation). Definitions of secondary outcomes and other documented variables are listed in Supplementary Table 4.

Safety assessments were conducted throughout the duration of the study. Any serious AE during treatment or FU was reported to the main study center within 24 hours to guarantee the registration of disproportionately frequent safety problems. For an objective assessment, all AEs were also categorized according to the AGREE (Adverse Events in Gastrointestinal Endoscopy) classification.[31]

Sample Size

The hypothesis of this study was that the resection of nonpedunculated colorectal polyps ≥2 cm by cold snare EMR is associated with a reduced major AE rate compared with hot resection. Estimated rates for major AEs were 2.1% for cold snare EMR[28,32] and 8.2% for hot snare EMR.[33] The difference of 6% was considered clinically relevant, with a significant improvement in patient safety. To detect this difference with a power ($1 - \beta$) of 80% and a significance level (α) of 5%, we calculated a sample size of 214 cases per group (including an estimated dropout rate of 5%). The trial was stopped earlier according to predefined rules after a planned interim analysis, which was conducted after recruitment of the first 214 cases with available 4-month FU. The difference between the groups was 7.6% at that point, which was well above the original assumption and the rate of dropout from ITT analysis was 7.9%. The recalculated sample size based on these (also clinically significant) results was 157 cases per group, a boundary that had already been crossed after 25 months of recruitment. Sample size calculation was performed using powerandsamplesize.com calculators (HyLown Consulting LLC).

Statistical Analysis

All statistical analyses were carried out using R, version 4.1.2 (R Core Team) and R Studio, version 2022.07.0 (Posit) software and were performed in the ITT and PP datasets. The ITT set included all randomized patients. The PP set excluded cases in which the allocated intervention was not carried out as planned (ie, conversion of resection technique or other protocol violation). Data on primary and secondary outcomes, as well as accessory data, were grouped and analyzed according to the randomization. Categorical outcomes were analyzed using the 2-sided χ^2 or Fisher exact test and were expressed as absolute

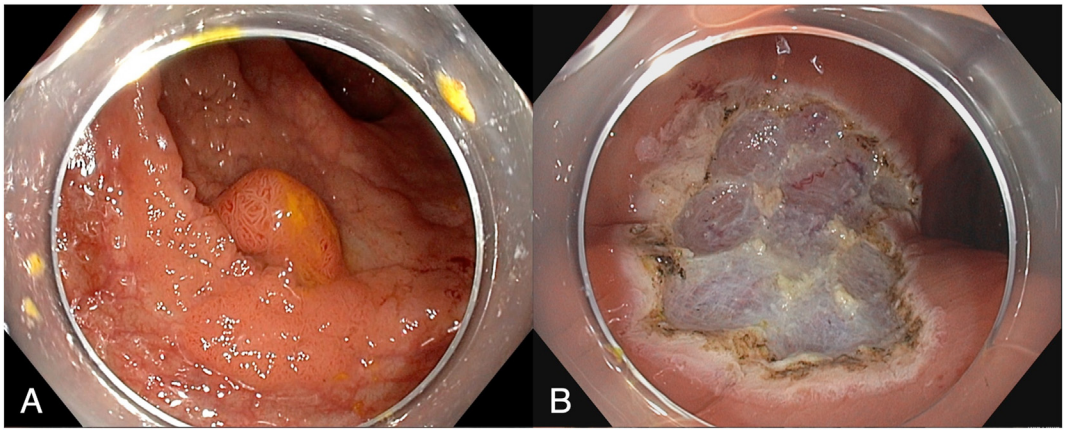

Figure 2. LST nodular-mixed type in the ascending colon before (*A*) and after (*B*) hot snare piecemeal EMR with margin coagulation.

and relative frequencies with 95% CIs and odds ratios (OR). ORs were corrected according to Haldane and Anscombe in case of 0 cell count. Continuous outcomes were compared using the Mann-Whitney U test and were presented as mean ± SD or median (range) and 95% CI. Missing values were reported but no imputation for missing data was performed. A P value <.050 (2-sided) was considered statistically significant.

Univariable and multivariable analysis was performed to identify independent predictors for major AEs and residual/recurrent adenoma/neoplasia. Age; sex; American Society of Anesthesiologists classification; anticoagulation; operators; low-, middle-, and high-volume centers; localization; lesion size; submucosal injection; number of pieces; intraprocedural bleeding; prophylactic treatments; clipping of vessels; clip closure of the resection site; level of difficulty; and histology were assessed as possible predictors. At first, a univariable logistic regression model (generalized linear model; rms package in R) was used and then a multivariable logistic regression model was used, including those factors that were associated with the outcome of interest in the univariable analysis ($P < .100$).

A scheduled close-out monitoring was carried out by an independent monitoring committee after termination of recruitment and 4-month FU.

All authors had access to the study data and reviewed and approved the final manuscript. The funder of the study (Gastroenterology Foundation, Küsnacht, Switzerland) had no role in the study design, data collection, analysis and interpretation, or writing of the report.

ENDOSCOPY

Results

Baseline Data and Clinical Characteristics

Between June 7, 2021 and July 17, 2023, there were 401 eligible polyps in 368 patients identified for the study (Figure 3). Characteristics and performance of the participating centers are provided in Supplementary Table 5. Five polyps (1.2%) were excluded during the procedure, as they did not meet the inclusion criteria (pretreated lesions in 3 cases and pedunculated polyps in 2 cases). As shown in Table 1, a total of 396 polyps in 363 patients (188 male patients [51.8%] and 175 female patients [48.2%]; mean ± SD age, 65.87 ± 10.50 years) were randomized and enrolled for the ITT analysis. Eighty-two participants (22.6%) received antiplatelet or anticoagulant therapy (details in Supplementary Table 6) with a significantly higher rate in the hot snare group (19.0% vs 28.1%; $P = .038$). The mean ± SD greater diameter of the lesions was of 3.01 ± 1.02 cm (range, 2.0–8.0 cm); 69.2% of the lesions were in the cecum and ascending colon. Morphologic assessment revealed LST granular homogenous type in 31.8% and suspected SSL in 25.0%. After histologic evaluation, 35.4% were in fact SSL or hyperplastic and 45.7% were adenomas with low-grade dysplasia (Table 1, further histologic details in Supplementary Table 7).

A total of 370 polyps were eligible for PP analysis (Figure 3). Reasons for noneligibility were conversion in 20 cases (15 [7.8%] in the cold and 5 [2.5%] in the hot group) and violation of the study protocol in 6 cases (5 [2.6%] in the cold and 1 [0.5%] in the hot group). Cold resection was converted to hot in 14 cases and to endoscopic full-thickness resection in 1 case. The hot snare was converted to endoscopic full-thickness resection in 3 cases and to endoscopic submucosal dissection and cold resection in 1 case each (Supplementary Table 8). As the reason for conversion, technical difficulties were stated in all cases. For patient and lesion details in the PP dataset, see Supplementary Table 9.

The technical success rate was 92.2% (n = 178 of 193; 95% CI, 87.5%–95.3%) in the cold and 97.5% (n = 198 of 203; 95% CI, 94.4%–98.9%) in the hot group ($P = .022$; OR, 0.30; 95% CI, 0.11–0.84). There was no significant difference in mean ± SD resection speed (22.59 ± 16.68 cm^2/h; 95% CI, 20.19–24.98 cm^2/h vs 21.72 ± 19.22 cm^2/h; 95% CI, 19.04–24.40 cm^2/h; $P = .281$). Technical data including the used snares are summarized in Supplementary Table 10. Submucosal injection was performed in 73.1% in the cold group and 95.1% in the hot group ($P < .001$), rates of en bloc resection were 2.1% and 8.4% ($P < .001$). The majority of cold snares were smaller than the hot snares, with significantly more resections in more than 5 pieces (68.9% vs 45.8%; $P < .001$), respectively. Prophylactic clipping was performed in 18.7% in the cold group and in 37.4% in the hot group ($P < .001$), clip closure of the resection site was performed in 13.5% and 28.1% ($P < .001$), prophylactic coagulation of blood vessels was performed in 0.5% and 17.7% ($P < .001$), and coagulation of the entire margin was performed in 1.6% and 30.5% ($P < .001$), respectively.

The following are the results of the ITT analysis for the most relevant outcome parameters.

Primary Outcome

The rates of major AEs were 1.0% (n = 2 of 193; 95% CI, 0.2%–3.7%) in the cold EMR group and 7.9% (n = 16 of 203; 95% CI, 4.9%–12.4%) in the hot EMR group ($P = .001$; OR, 0.12; 95% CI, 0.03–0.54) in the per-polyp analysis (Table 2). The per-patient analysis yielded analogous results (Supplementary Table 11). All major AEs were clearly attributable to a single polyp. Only 1 major AE occurred in a patient with more than 1 resected polyp, which was a perforation that was diagnosed and treated interprocedurally.

Secondary Outcomes

Adverse events. Results of the per-polyp analysis for the major AE subcategories are presented in Table 2 and Supplementary Table 12. Perforation rates were 0% (n = 0 of 193; 95% CI, 0.0%–1.8%) in the cold EMR group and 3.9% (n = 8 of 203; 95% CI, 2.0%–7.6%) in the hot EMR group ($P = .007$; OR, 0.06; 95% CI, 0.003–1.04). All perforations were located in the right colon and occurred intraprocedurally in 7 cases and within 24 hours in 1 case. Previous lesion assessment was LST granular type in 5 cases and SSL in 3 cases, with diameters between 2.5 and 6.0 cm. Five perforations were type 3 and 3 perforations were type 4 according to the Sydney classification. All intraprocedural perforations were successfully treated endoscopically by means of clipping and the delayed perforation by means of

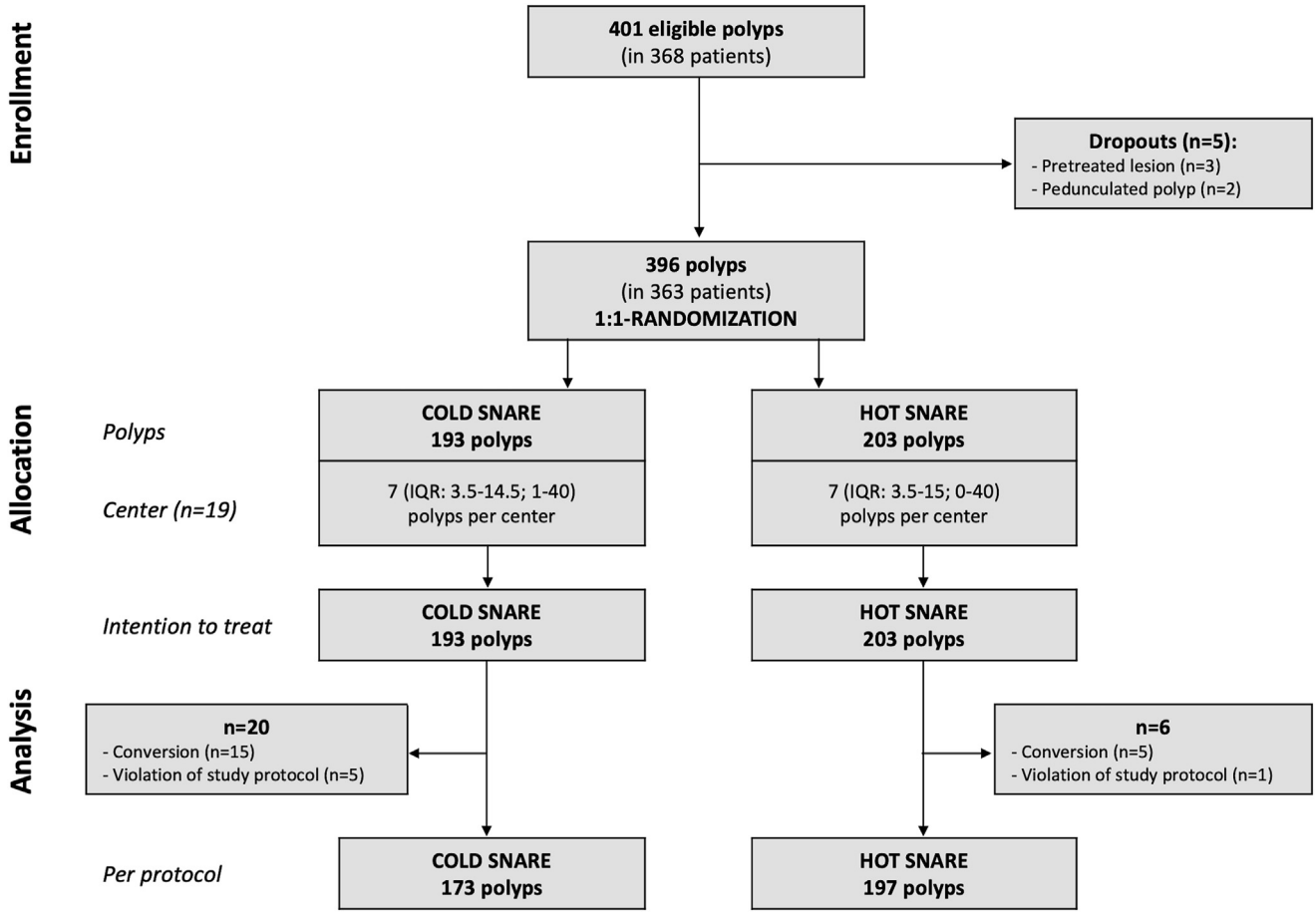

Figure 3. Trial flow chart.

inpatient monitoring and antibiotic therapy. In 1 case, both a perforation and postprocedural bleeding occurred. Rates of postprocedural bleeding were 1.0% (n = 2 of 193; 95% CI, 0.2%–3.7%) in the cold EMR group and 4.4% (n = 9 of 203; 95% CI, 2.3%–8.2%) in the hot EMR group (P = .040; OR, 0.23; 95% CI, 0.05–1.06). Successful endoscopic treatment was performed in 9 cases and prolonged inpatient monitoring in 2 cases. Other AEs are provided in Table 2 and Supplementary Table 13. Significant differences in favor of cold resection were found in intraprocedural bleedings. The rates of postpolypectomy syndromes were not significantly different with 6 of 193 (3.1%) in the cold and 9 of 203 (4.4%) in the hot group (P = .490). No patient received surgical therapy due to AEs and no treatment-related deaths were observed. The per-patient analysis yielded analogous results (Supplementary Table 11).

Residual/recurrent neoplasia at the first follow-up examination. Data regarding residual adenoma/neoplasia were available in 351 cases (88.6%); in 346 at endoscopic FU and in 5 specimens after surgical resection. Reasons for surgery were histology of adenocarcinoma (2 cases in the cold group and 3 cases in the hot group). Mean ± SD FU period was 4.35 ± 2.14 months (range, 1–17 months). In the ITT dataset, the rate of recurrent or residual neoplasia was 23.7% (n = 42 of 177; 95% CI, 18.1%–30.5%) after cold EMR and 13.8% (n = 24 of 174; 95% CI, 9.4%–19.7%) after hot EMR (P = .020; OR, 1.94; 95% CI, 1.12–3.38) (Table 2, for the per-patient analysis, Supplementary Table 11). In 9 of 66 cases (13.6%) residual neoplasia was diagnosed histologically from biopsies of inconspicuous scars. Of the endoscopically diagnosed residual lesions, 96.8% were re-treated by means of endoscopic resection. Two cases from the initial cold snare group received surgical treatment due to malignant histology in the specimen from the FU examination (Supplementary Table 14 for details).

For residual/recurrent neoplasia, a post-hoc subgroup analysis according to morphologic criteria (SSL/LST classification) was done (Table 3). For suspected SSL, the rate of residual neoplasia was 8.3% (n = 4 of 48; 95% CI, 3.3%–19.5%) in the cold EMR group and 4.8% (n = 2 of 42; 95% CI, 1.3%–15.8%) in the hot EMR group (P = .681). However, the macroscopic assessment of SSLs or hyperplastic polyps was confirmed by histopathology in only 81.8%, and only 70.7% of the histopathologically diagnosed SSLs were previously classified correctly by the examiner. For the LST, only the nodular-mixed types had significantly different rates of residual adenoma, with 40.5% (n = 15 of 37; 95% CI, 26.3%–56.5%) in the cold group and 14.3% (n = 6 of 42; 95% CI, 6.7%–27.8%) in the hot group (P = .011; OR, 3.97; 95% CI, 1.38–12.80). But it must be added that after histopathologic examination of the LST nongranular type,

Table 1. Patient and Lesion Characteristics (Intention-to-Treat Dataset)

Characteristic	All (n = 396 polyps; n = 363 patients)	Cold snare EMR (n = 193 polyps; n = 184 patients)	Hot snare EMR (n =203 polyps; n = 192 patients)	*P* value
Patient age, *y*, mean ± SD (range)	65.87 ± 10.50 (21–92)	65.11 ± 11.04 (21–92)	66.34 ± 10.36 (21–86)	.286[a]
Patient sex, n (%)				.186[b]
Male	188/363 (51.8)	90/184 (48.9)	107/192 (55.7)	
Female	175/363 (48.2)	94/184 (51.1)	85/192 (44.3)	
Patient ASA grade, mean ± SD (range)	1.68 ± 0.59 (1–3)	1.68 ± 0.61 (1–3)	1.69 ± 0.57 (1–3)	.801[a]
I, n (%)	139/363 (38.3)	72/184 (39.1)	70/192 (36.5)	
II, n (%)	200/363 (55.1)	98/184 (53.3)	111/192 (57.8)	.598[b]
III, n (%)	24/363 (6.6)	14/184 (7.6)	11/192 (5.7)	
Antiplatelet/anticoagulant therapy, n (%)	82/363 (22.6)	35/184 (19.0)	54/192 (28.1)	**.038**[b]
Bowel cleaning score (BBPS), mean ± SD (range)	7.44 ± 1.54 (4–9)	7.38 ± 1.54 (4–9)	7.47 ± 1.53 (4–9)	.539[a]
Greater lesion diameter, *cm*, mean ± SD (range)	3.01 ± 1.02 (2.0–8.0)	3.05 ± 1.07 (2.0–7.0)	2.98 ± 0.98 (2.0–8.0)	.803[a]
Lesion size, cm^2, mean ± SD (range)	5.81 ± 4.37 (0.79–28.27)	6.02 ± 4.73 (0.79–27.49)	5.60 ± 4.00 (1.18–28.27)	.805[a]
Lesion localization, n (%)				.794[b]
Cecum	109/396 (27.5)	57/193 (29.5)	52/203 (25.6)	
Ascending colon	165/396 (41.7)	77/193 (39.9)	88/203 (43.3)	
Transverse colon	71/396 (17.9)	36/193 (18.7)	35/203 (17.2)	
Descending colon	24/396 (6.1)	12/193 (6.2)	12/203 (5.9)	
Sigmoid colon	17/396 (4.3)	8/193 (4.1)	9/203 (4.4)	
Rectum	10/396 (2.5)	3/193 (1.6)	7/203 (3.4)	
Paris classification, n (%)				.933[c]
0-Is	33/396 (8.3)	17/193 (8.8)	16/203 (7.9)	
0-IIa	305/396 (77.0)	146/193 (75.6)	159/203 (78.3)	
0-IIb	4/396 (1.0)	2/193 (1.0)	2/203 (1.0)	
0-Is+IIa	34/396 (8.6)	18/193 (9.3)	16/203 (7.9)	
0-IIa+Is	14/396 (3.5)	6/193 (3.1)	8/203 (3.9)	
0-IIa+Ic	0	0	0	
0-IIc+IIa	0	0	0	
0-IIa+IIc	6/396 (1.5)	4/193 (2.1)	2/203 (1.0)	
Laterally spreading tumor, n (%)				.937[b]
Granular-type homogenous	126/396 (31.8)	60/193 (31.1)	66/203 (32.5)	
Granular-type nodular-mixed	88/396 (22.2)	42/193 (21.8)	46/203 (22.7)	
Nongranular-type flat elevated	73/396 (18.4)	34/193 (17.6)	39/203 (19.2)	
Nongranular-type pseudodepressed	10/396 (2.5)	5/193 (2.6)	5/203 (2.5)	
Suspected SSL	99/396 (25.0)	52/193 (26.9)	47/203 (23.2)	
Histology, n (%)				
SSL/hyperplastic polyps	140/396 (35.4)	76/193 (39.4)	64/203 (31.5)	.358[c]
Adenoma LGD	181/396 (45.7)	80/193 (41.5)	101/203 (49.8)	
Adenoma HGD	67/396 (16.9)	33/193 (17.1)	34/203 (16.7)	
Adenocarcinoma in adenoma	8/396 (2.0)	4/193 (2.1)	4/203 (2.0)	
Tubular adenoma	146/396 (36.9)	66/193 (34.2)	80/203 (39.4)	.892[b]
Adenoma with villous components	102/396 (25.8)	47/193 (24.4)	55/203 (27.1)	

NOTE. Significant *P* values are in boldface.
ASA, American Society of Anesthesiologists classification; BBPS, Boston Bowel Preparation Scale; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NICE, Narrow-Band Imaging International Colorectal Endoscopic classification; JNET, Japanese Narrow-Band Imaging Expert Team classification.
[a]Wilcoxon-Mann-Whitney U test.
[b]χ^2 test.
[c]Fisher exact test.

Table 2. Outcomes in the Intention-to-Treat and Per-Protocol Analysis

	ITT					
	Cold snare EMR (n = 193)		Hot snare EMR (n = 203)			
Variable	n (%)	95% CI	n (%)	95% CI	*P* value	Odds ratio (95% CI)
Major AE	2 (1.0)	0.2–3.7	16 (7.9)	4.9–12.4	**.001**[a]	**0.12** (0.03–0.54)
Perforation	0 (0)	0.0–1.8	8 (3.9)	2.0–7.6	**.007**[b]	**0.06** (0.003–1.04)
Postprocedural bleeding	2 (1.0)	0.2–3.7	9 (4.4)	2.3–8.2	**.040**[a]	**0.23** (0.05–1.06)
Intraprocedural bleeding	27 (14.0)	9.8–19.5	46 (22.7)	17.4–28.8	**.026**[a]	**0.56** (0.33–0.94)
Postpolypectomy syndrome	6 (3.1)	1.4–6.6	9 (4.4)	2.3–8.2	.490[a]	0.69 (0.24–1.98)
Residual/recurrent adenoma (first FU)	42/177 (23.7)	18.1–30.5	24/174 (13.8)	9.4–19.7	**.020**[b]	**1.94** (1.12–3.38)
	PP					
	Cold snare EMR (n = 173)		Hot snare EMR (n = 197)			
Variable	n (%)	95% CI	n (%)	95% CI	*P* value	Odds ratio (95% CI)
Major AE	2 (1.2)	0.3–4.1	15 (7.6)	4.6–12.1	**.003**[a]	**0.14** (0.03–0.63)
Perforation	0 (0)	0.0–2.1	8 (4.1)	2.1–7.8	**.008**[b]	**0.06** (0.004–1.12)
Postprocedural bleeding	2 (1.2)	0.3–4.1	8 (4.1)	2.1–7.8	.112[a]	0.28 (0.06–1.32)
Intraprocedural bleeding	18 (10.4)	6.7–15.8	44 (22.3)	17.1–28.6	**.002**[a]	**0.40** (0.22–0.73)
Postpolypectomy syndrome	6 (3.5)	1.6–7.4	9 (4.6)	2.4–8.5	.592[a]	0.75 (0.26–2.15)
Residual/recurrent adenoma (first FU)	38/160 (23.8)	17.8–31.0	20/168 (11.9)	7.8–17.7	**.006**[b]	**2.30** (1.28–4.17)

NOTE. Significant *P* values and odds ratio are in boldface.
[a]χ^2 test.
[b]Fisher exact test.

28.9% were, in fact, SSL or hyperplastic and only 4.8% were malignant.

The results in the PP datasets were similar to the ITT analyses (Tables 2 and 3 and Supplementary Table 11).

Predictors for Major Adverse Events and Residual/Recurrent Neoplasia

The only independent predictor for major AEs in univariable or multivariable regression analysis was a polyp diameter ≥4 cm (OR, 3.37; 95% CI, 1.25–9.09) (Supplementary Table 15). Independent predictors for residual/recurrent neoplasia in univariable or multivariable regression analysis were polyp diameter ≥4 cm (OR, 2.47; 95% CI, 1.21–5.03) and histology of adenoma with high-grade dysplasia or carcinoma (OR, 2.92; 95% CI, 1.22–7.00) (Supplementary Table 16).

Discussion

To our knowledge, this is the first RCT comparing cold and hot snare resection of nonpedunculated colorectal polyps ≥20 mm. The hypothesis for the study was that cold snare resection may reduce post-EMR complications with less evident differences in rates of residual neoplasia. This rationale was based on mostly retrospective case series and cohort studies. Major AEs after hot EMR of polyps ≥2 cm were summarized in a review of the ASGE with perforation rates of 0.1%–2.2% (pooled rate, 1.1%), and postendoscopic bleedings of 0.2%–8.4% (pooled rate, 3.7%).[14] These data are concordant with our major AE rate of 7.9%. Such complications require additional interventions and often patient readmission or prolongation of hospital stay.[34] This makes measures to avoid major AEs and associated sequelae and costs worthwhile, especially because outpatient performance of EMR is standard in some countries and will be mandated increasingly in others.

Cold snare resection is a promising technique to make EMR safer. The superiority of the cold snare in terms of postprocedural bleeding was initially shown for polyps <10 mm[35,36] and recently for lesions of 10–20 mm as well.[37] In larger, flat polyps (≥20 mm), studies mostly included SSL and again, complication rates were lower compared with hot EMR.[22,32] Postprocedural bleeding rates varied between 0% and 3.8% and perforations were close to 0 in all trials and meta-analyses. The same was reported from a retrospective observational study in the duodenum.[38]

These results were confirmed by our RCT in both ITT and PP analyses, with a reduction of major AEs by >85%, that is, from 7.9% to 1.0%. This difference was even higher

Table 3. Subgroup Analysis for Residual/Recurrent Adenoma/Neoplasia at the First Follow-up Examination (Intention-to-Treat and Per-Protocol Datasets)

	Cold snare EMR		Hot snare EMR			
Variable	n (%)	95% CI	n (%)	95% CI	*P* value	Odds ratio (95% CI)
ITT dataset						
Suspected SSL	4/48 (8.3)	3.3–19.5	2/42 (4.8)	1.3–15.8	.681[b]	1.75 (0.30–14.75)
LST granular-type homogeneous	17/57 (29.8)	19.55–42.6	12/57 (21.1)	12.5–33.3	.116[a]	1.58 (0.67–3.81)
LST nodular mixed-type	15/37 (40.5)	26.3–56.5	6/42 (14.3)	6.7–27.8	**.011**[a]	**3.97** (1.38–12.80)
LST nongranular-type	6/35 (17.1)	8.1–32.7	4/33 (12.1)	4.8–27.3	.735[b]	1.48 (0.37–6.56)
PP dataset						
Suspected SSL	4/44 (9.1)	3.6–21.2	2/41 (4.9)	1.3–16.1	.677[b]	1.87 (0.33–15.84)
LST granular-type homogeneous	15/51 (29.4)	19.1–43.7	11/56 (19.6)	11.3–31.8	.261[a]	1.69 (0.69–4.25)
LST nodular mixed-type	13/32 (40.6)	25.5–57.7	5/41 (12.2)	5.3–25.5	**.007**[a]	**4.74** (1.52–17.09)
LST nongranular-type	6/33 (18.2)	8.6–34.4	2/30 (6.7)	1.8–21.3	.261[b]	2.93 (0.59–23.67)

NOTE. Significant *P* values and odds ratio are in boldface.
[a]Fisher exact test.
[b]χ^2 test.

than originally assumed, so that the recruitment could be terminated prematurely. No perforations occurred with cold EMR. The difference to the 8 cases in the standard group was statistically significant and clinically relevant, even if all of the latter cases were managed endoscopically or conservatively. Specific features of the lesions regarding morphology or size that might help to avoid perforations were not evident. But the successful nonsurgical treatment of all cases confirms the results of a retrospective cohort study, in which surgery was not necessary in the majority of interventional perforations.[34] This has to be considered when the severity of perforations is assessed. In addition, postendoscopic bleedings were less frequent in the cold EMR group, with 1.0% vs 4.4%. The fact that more anticoagulants were prescribed in the hot snare group may have contributed to this result but, in regression analysis, anticoagulation was no predictor for major AEs. It has been reported that prophylactic clip closure of the resection area after piecemeal EMR also reduces postendoscopic bleedings, particularly in the right colon.[18–20] In our study, neither partial nor complete closure of the resection site was a predictive factor for major AEs. However, disadvantages of this technique are the time and cost involved and the technical difficulty closing larger resection areas completely. In comparison, cold snare resection might be the more feasible option for prevention of delayed bleeding.

Postpolypectomy syndrome was not included in the major AE category, in accordance with the recent ASGE review.[14] Nevertheless, even if included in this category, major AE rates would still be significantly lower with the cold snare ($P = .003$), that is, 8 of 193 (4.1%) vs 25 of 203 (12.3%). These results make cold snare resection particularly interesting for outpatient management of large flat polyps. The only independent predictor for major AE in univariable or multivariable regression analysis was a polyp diameter ≥4 cm, which has already been demonstrated for hot snare EMR.[33] Additional predictive factors reported in other series were not found in our trial.

For the near elimination of perforations with the cold snare, several reasons can be stated: With these snares, it is almost impossible to cut through the proper muscle layer, and only a small tissue volume can be resected due to the limited snare size. The lack of a thermal effect on the muscle layer may also prevent delayed perforation. Another reason is the removal of less submucosal tissue with the cold snare (51 vs 933 μm), which might also contribute to the lower risk of delayed bleeding.[39] It has been found that histologic damage of submucosal arteries is also reduced from 39% to 22%, with a significantly lower postprocedural bleeding rate compared with hot resection.[21] It can only be speculated whether vessel defect closure mechanisms after cold rupture may function better than cutting with current.

Regarding minor AEs, also postpolypectomy syndrome, in its full extent, requires additional measures and prompts prolonged hospital stay. It is attributed to thermal damage of the proper muscle layer regressing under conservative therapy.[40] The fact that, in our study, postpolypectomy syndromes occurred with the cold snare at a similar level suggests that other causes, like size of the resection area, may play a greater pathophysiologic role than previously thought. Abdominal pain after hot EMR suggesting postpolypectomy syndrome occurred in 5.2% of the cases in a large prospective study,[41] which is concordant to our data. The lower incidence in the ASGE review of 0.003%–1% can be attributed to variable definitions and well-known differences between retrospective databases and prospective randomized trials. In addition, intraprocedural bleeding is subject to great variability in definition and perception. Self-limiting bleeding during cold resection is frequent. The definition in our trial included the need for treatment and the rate was significantly lower in the cold resection group. This is different from a meta-analysis of small polyp resections, where rates of intraprocedural bleeding were higher for the cold snare in comparison with standard therapy with 6.6% vs 3.3%, perhaps again due to definition and other methodologic issues.[42]

Retrospective data already indicated that the substantial reduction in AE by cold resection might be accompanied by a higher rate of residual/recurrent adenoma. In SSL, rates of residual neoplasia were not different between cold and hot resection,[22] but this could be the case for adenomas. Results of retrospective studies on this subject are contradictory. In 1 series of 204 polyps ≥2 cm, the rate of residual neoplasia was only 5.5%, but two-thirds of polyps were SSLs.[27] In another study with 310 large polyps, the rate was 34%; only 20% were SSL or hyperplastic.[43] Finally, a smaller series of flat polyps ≥1 cm (n = 73) with 80% adenomas had a rate of residual adenoma of 9.7%. Fifty-one percent of these lesions were ≥2 cm, and all cases (n = 7) occurred in this group only. This resulted in a residual adenoma rate of 25% in this very small subgroup.[44] These retrospective data suggest that the rate of recurrence/residual adenoma after cold resection could be well over 20%. This is in line with results from the duodenum, where recurrence was not higher in a first retrospective comparative study,[38] but was substantial in 2 other trials.[45,46]

The higher rate of residual adenoma/neoplasia after cold EMR of flat colorectal polyps ≥2 cm was confirmed by our RCT with an increase of 10% compared with hot resection. Reasons are manyfold, such as the more difficult assessment of the resection area due to frequent capillary bleeding and the higher number of resection pieces.[47] The rate of residual adenoma of 14% in the hot EMR group is similar to a recent review, where it was 11% with a broad range between 5% and 30%.[48] One limitation of our study is the not systematically performed margin coagulation. This has recently been found to reduce residual/recurrent neoplasia to <5%–10%.[8,9,48–52] During the planning of this study in 2020, the evidence for this technique was not as strong and, in accordance with the guidelines at that time,[2,29] it was decided to leave this to the discretion of the endoscopist after hot snare EMR. In our cohort, margin coagulation was performed in 65 cases, and it was not an independent predictive factor for residual/recurrent neoplasia in univariable or multivariable analysis. Reasons could be that it was not systematically recorded whether the margin coagulation was incomplete or complete and that this technique also has a learning curve. However, if the rate of residual adenoma would have been further reduced by margin coagulation, the difference would be even more pronounced in favor of hot EMR. However, our rate of residual adenoma after cold snare resection was similar to previous German reports of hot snare EMR without margin coagulation.[4,41] This could indicate that residual neoplasia might be more a matter of additional margin treatment and less of cold or hot resection. Furthermore, most cases of residual adenoma at short-term FU were small and easy to treat, so different rates may not be so relevant. However, frequent colonoscopies should be avoided because patient adherence may be variable and limited. Whether below a certain rate of residual adenoma a systematic early FU is expendable is a matter of discussion, as many database studies found that advanced adenomas still have a worse prognosis regarding interval cancers.[53,54] In addition, the recurrence rate could still be underrated in our study, as the median FU interval was 4.35 (±2.14) months, which is <6 months as the optimal interval for the detection of residual adenoma.[47] This could also be the reason for the rate of residual adenoma of 13.6% in inconspicuous scars, which is higher than the 6.4%–6.7% in recent studies.[55,56] Irrespectively, improvements of cold EMR are indicated to make it more effective. Technical modifications of the cold or hybrid snares, which enable a cut through larger tissue pieces without additional maneuvers, could improve technical success and recurrence rates in the future. By combining this with measures such as margin coagulation, we might arrive at a safe, effective, and low-cost alternative to the current standard for large polyps. These issues should be the topic of further studies.

The lower technical success rate of the cold snare and also data of our post-hoc subgroup analysis suggest that not every lesion is equally suitable for cold snare EMR, although the value of the latter evaluation is limited and may be regarded as hypothesis-generating only. Suspected SSLs seem to be best suited for cold snare resection because recurrence rates were similar in both groups. This is in concordance with previous retrospective series,[22,38] although the macroscopic assessment of SSL was correct in only 71% of the cases. Very flat and homogenous adenomatous lesions, such as granular-type LST, may also be suitable for the cold snare. The largest difference in favor of hot resection was seen in the mixed-type LST. The cold cut through advanced neoplasms and the resection in a superficial submucosal layer might not be the appropriate modality in these cases, especially when larger nodules are present. In addition, histology of advanced adenoma or carcinoma and polyp diameter ≥4 cm were independent predictors for residual neoplasia. Thus, another practical conclusion may be that lesions of a larger size and those with a complex morphology should be treated further by hot snare EMR with additional measures.

In addition, preinterventional optical assessment of polyps needs improvement, according to our data, with a high number of false-positive and false-negative SSL estimations. Imaging studies involving dedicated experts usually reach better results. But (possibly more representative) real-life data suggest a lower accuracy.[57] Whether artificial intelligence might improve diagnostic accuracy for the selection of suitable polyps for cold snare resection has to be studied further.

This study has some strengths and limitations. Strengths are the randomized controlled and multicentric design with a high case load, the systematic monitoring of delayed AEs and the reliable detection of residual adenoma by also taking biopsies from inconspicuous scars during endoscopic FU. The real-life approach of the study with various options of therapeutic and prophylactic measures in accordance with the guidelines[2,29] can be seen as a limitation, as a lower degree of standardization probably results in a higher technical variability and possible bias. To consider this problem, the predictive value of the individual techniques on the outcome was estimated by regression analyses. Other limitations are the impossibility of blinding the endoscopists to the group allocation and the small and quite similar

number of main outcomes, leading to a certain statistical fragility. Finally, high rates of right colonic lesions and SSL suggest a probable referral bias, and some subjective morphology-based criteria (eg, size and LST classification) are prone to errors, a problem we share with almost all other publications on this topic. Both might lower the generalizability of the results.

In summary, results of our RCT indicate that cold resection of large nonpedunculated polyps is safer than hot EMR, with an almost complete elimination of major AE. This must be balanced against a higher rate of residual adenoma. For SSL and selected groups of adenomas that are not too large or suspicious for advanced histology, this disadvantage appears to be less relevant. Future studies should identify which technical developments are necessary to further improve outcomes and cost-effectiveness of polypectomy (eg, by combining the safety of the cold snare with measures to reduce recurrence) and which allocation strategies to the different resection methods are most effective.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2024.05.013.

References

1. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687–696.
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. Moss A, Williams SJ, Hourigan LF, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut 2015;64:57–65.
4. Seidel J, Färber E, Baumbach R, et al. Complication and local recurrence rate after endoscopic resection of large high-risk colorectal adenomas of >/=3 cm in size. Int J Colorectal Dis 2016;31:603–611.
5. Cipolletta L, Rotondano G, Bianco MA, et al. Endoscopic resection for superficial colorectal neoplasia in Italy: a prospective multicentre study. Dig Liver Dis 2014;46:146–151.
6. Heresbach D, Kornhauser R, Seyrig JA, et al. A national survey of endoscopic mucosal resection for superficial gastrointestinal neoplasia. Endoscopy 2010;42:806–813.
7. Woodward TA, Heckman MG, Cleveland P, et al. Predictors of complete endoscopic mucosal resection of flat and depressed gastrointestinal neoplasia of the colon. Am J Gastroenterol 2012;107:650–654.
8. Sidhu M, Shahidi N, Gupta S, et al. Outcomes of thermal ablation of the mucosal defect margin after endoscopic mucosal resection: a prospective, international, multicenter trial of 1000 large nonpedunculated colorectal polyps. Gastroenterology 2021;161:163–170.
9. Rex DK, Haber GB, Khashab M, et al. Snare tip soft coagulation vs argon plasma coagulation vs no margin treatment after large nonpedunculated colorectal polyp resection:a randomized trial. Clin Gastroenterol Hepatol 2023;21:S1542–S3565.
10. 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.e1.
11. Rodriguez Sanchez J, Alvarez-Gonzalez MA, Pellise M, et al. Underwater versus conventional EMR of large nonpedunculated colorectal lesions: a multicenter randomized controlled trial. Gastrointest Endosc 2023;97:941–951.e2.
12. Bar-Yishay I, Shahidi N, Gupta S, et al. Outcomes of deep mural injury after endoscopic resection: an international cohort of 3717 large non-pedunculated colorectal polyps. Clin Gastroenterol Hepatol 2022;20:e139–e147.
13. Arezzo A, Passera R, Marchese N, et al. Systematic review and meta-analysis of endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions. United European Gastroenterol J 2016;4:18–29.
14. Kothari ST, Huang RJ, Shaukat A, et al. ASGE review of adverse events in colonoscopy. Gastrointest Endosc 2019;90:863–876.e33.
15. Elliot TR, Tsiamoulos ZP, Thomas-Gibson S, et al. Factors associated with delayed bleeding after resection of large nonpedunculated polyps. Endoscopy 2018;50:790–799.
16. Metz AJ, Bourke MJ, Moss A, et al. Factors that predict bleeding following endoscopic mucosal resection of large colonic lesions. Endoscopy 2011;43:506–511.
17. Burgess NJ, Metz AJ, Williams SJ, et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. Clin Gastroenterol and Hepatol 2014;12:651–661.
18. Albéniz E, Álvarez MA, Espinós JC, et al. Clip closure after resection of large colorectal lesions with substantial risk of bleeding. Gastroenterology 2019;157:1213–1221.e4.
19. Gupta S, Sidhu M, Shahidi N, et al. Effect of prophylactic endoscopic clip placement on clinically significant post-endoscopic mucosal resection bleeding in the right colon: a single-centre, randomised controlled trial. Lancet Gastroenterol Hepatol 2022;7:152–160.
20. Forbes N, Gupta S, Frehlich L, et al. Clip closure to prevent adverse events after EMR of proximal large nonpedunculated colorectal polyps: meta-analysis of individual patient data from randomized controlled trials. Gastrointest Endosc 2022;96:721–731.e2.
21. Horiuchi A, Nakayama Y, Kajiyama M, et al. Removal of small colorectal polyps in anticoagulated patients: a prospective randomized comparison of cold snare and conventional polypectomy. Gastrointest Endosc 2014;79:417–423.

22. 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;70:1691–1697.
23. von Renteln D, Djinbachian R, Benard F, et al. Incomplete resection of colorectal polyps of 4-20 mm in size when using a cold snare, and its associated factors. Endoscopy 2023;55:929–937.
24. Muniraj T, Sahakian A, Ciarleglio MM, et al. Cold snare polypectomy for large sessile colonic polyps: a single center experience. Gastroenterol Res Pract 2015175959.
25. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Ann Int Med 2010;152:726–732.
26. 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.
27. Papastergiou V, Paraskeva KD, Fragaki M, et al. Cold versus hot endoscopic mucosal resection for non-pedunculated colorectal polyps sized 6-10 mm: a randomized trial. Endoscopy 2018;50:403–411.
28. Mangira D, Cameron K, Simons K, et al. Cold snare piece meal endoscopic mucosal resection of large sessile colonic polyps ≥20mm (with video). Gastrointest Endosc 2020;91:1343–1352.
29. Schmiegel W, Buchberger B, Follmann M, et al. S3-leitlinie kolorektales karzinom. Z Gastroenterol 2017; 55:1344–1498.
30. Burgess NG, Bassan MS, McLeod D, et al. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. Gut 2017;66:1779–1789.
31. Nass KJ, Zwager LW, van der Vlugt M, et al. Novel classification for adverse events in GI endoscopy: the AGREE classification. Gastrointest Endosc 2022; 95:1078–1085.e8.
32. Chandrasekar VT, 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.
33. Heldwein W, Dollhopf M, Rösch T, et al. The Munich Polypectomy Study (MUPS): prospective analysis of complications and risk factors in 4000 colonic snare polypectomies. Endoscopy 2005;37:1116–1122.
34. Steinbrück I, Pohl J, Grothaus J, et al. Characteristics and endoscopic treatment of interventional and non-interventional iatrogenic colorectal perforations in centers with high endoscopic expertise: a retrospective multicenter study. Surg Endosc 2023;37:4370–4380.
35. Li D, Wang W, Xi 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.
36. Abuelazm M, Awad AK, Mohamed I, et al. Cold polypectomy techniques for small and diminutive colorectal polyps: a systematic review and network meta-analysis of randomized controlled trials. Curr Med Res Opin 2023;39:1329–1339.
37. Niu C, Bapaye J, Zhang J, et al. Systematic review and meta-analysis of cold snare polypectomy and hot snare polypectomy for colorectal polyps. J Gastroenterol Hepatol 2023;38:1458–1467.
38. Repici A, Capogreco A, Spadaccini M, et al. Cold versus hot EMR for large duodenal adenomas. Gut 2022; 71:1763–1765.
39. 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.
40. Kedia P, Waye JD. Colon polypectomy: a review of routine and advanced techniques. J Clin Gastroenterol 2013;47:657–665.
41. Knabe M, Pohl J, Gerges C, et al. Standardized long-term follow-up after endoscopic resection of large, nonpedunculated colorectal lesions: a prospective two-center study. Am J Gastroenterol 2014;109:183–189.
42. Jegadeesan R, Aziz M, Desai M, et al. Hot snare vs cold snare polypectomy for endoscopic removal of 4 – 10 mm colorectal polyps during colonoscopy: a systematic review and meta-analysis of randomized controlled studies. Endosc Int Open 2019;7:e708–e716.
43. Suresh S, Zhang J, Ahmed A, et al. Risk factors associated with adenoma recurrence following cold snare endoscopic mucosal resection of polyps ≥ 20 mm: a retrospective chart review. Endosc Int Open 2021; 9:e867–e873.
44. Piraka C, Saeed A, Waljee AK, et al. Cold snare polypectomy for non-pedunculated colon polyps greater than 1 cm. Endosc Int Open 2017;5:e184–e189.
45. Wang H, Sidhu M, Gupta S, et al. Cold snare EMR for the removal of large duodenal adenomas. Gastrointest Endosc 2023;97:1100–1108.
46. Wilson N, Abdallah M. Outcomes of cold snare endoscopic mucosal resection of nonampullary duodenal adenomas ≥1 cm: a multicenter study. Gastrointest Endosc 2024;99:971–980.e1.
47. Belderbos TD, Leenders M, Moons LMG, Siersema PD. Local recurrence after endoscopic mucosal resection of non-pedunculated colorectal lesions: systematic review and meta-analysis. Endoscopy 2014;46:388–402.
48. Rothermund C, Djinbachian R, Taghiakbari M, et al. Recurrence rates after endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. World J Gastroenterol 2022;28:4007–4018.
49. Nader SM, Lahr RE, Rex DK. Impact of margin thermal treatment after EMR of giant (≥40 mm) colorectal lateral spreading lesions. Gastrointest Endosc 2023; 97:544–548.
50. Djinbachan R, Pohl H, Rex DK, et al. Thermal ablation after endoscopic mucosal resection of large colorectal polyps: not only the margins, but also the base? Gut 2023;73:12–15.
51. Arisha MA, Scapa E, Wishahi E, et al. Impact of margin ablation after EMR of large nonpedunculated colonic polyps in routine clinical practice. Gastrointest Endosc 2023;97:559–567.

52. Jaques J, Schaefer M, Wallenhorst T, et al. Endoscopic en bloc versus piecemeal resection of large non-pedunculated colonic adenomas: a randomized comparative trial. Ann Intern Med 2024;177:29–38.
53. Duvvuri A, Chandrasekar VT, Srinivasan S, et al. Risk of colorectal cancer and cancer related mortality after detection of low-risk or high-risk adenomas, compared with no adenoma, at index colonoscopy: a systematic review and meta-analysis. Gastroenterology 2021; 160:1986–1996.e3.
54. Baille-Maxia S, Mangas-Sanjuan C, Ladabaum U, et al. Risk factors for metachronous colorectal cancer or advanced adenomas after endoscopic resection of high-risk adenomas. Clin Gastroenterol Hepatol 2023; 21:630–643.
55. Kandel P, Brand EC, Pelt J, et al. Endoscopic scar assessment after colorectal endoscopic mucosal resection scars: when is biopsy necessary (EMR Scar Assessment Project for Endoscope (ESCAPE) trial). Gut 2019;68:1633–1641.
56. Desomer L, Tutticci N, Tate DJ, et al. A standarized imaging protocol is accurate in detecting recurrence after EMR. Gastrointest Endosc 2017;85:518–526.
57. van de Wetering AJP, Meulen LWT, Bogie RMM, et al. Optical diagnosis of diminutive polyps in the Dutch Bowel Cancer Screening Program: are we ready to start? Endosc Int Open 2020;8:e257–e265.

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Conflicts of interest

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Data Availability

There are currently no plans to make data available to other researchers. In the future, we may make data available to be able to carry out valid evaluations with higher case loads (eg, for individual subgroups) together with other study groups.