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

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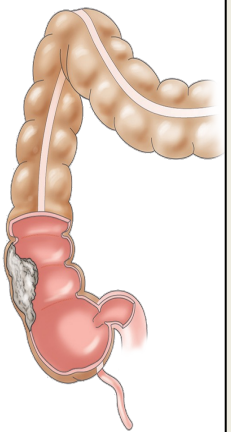
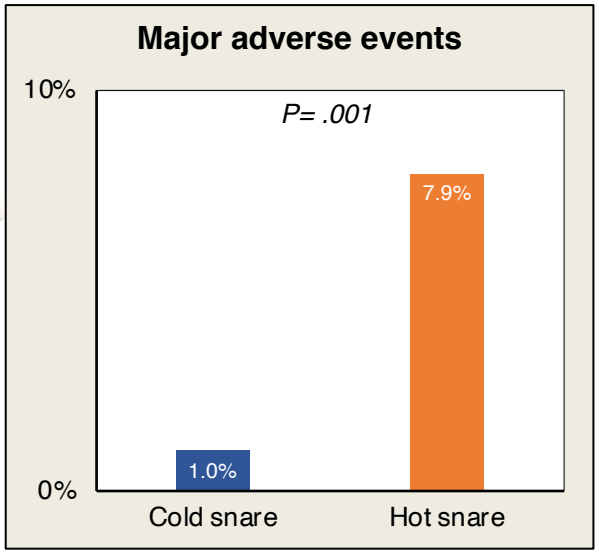
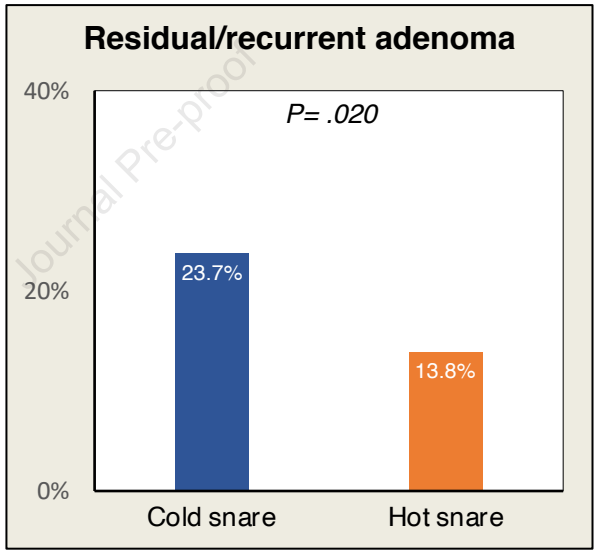
Major adverse events are a relevant problem of hot snare-EMR of non-pedunculated colorectal polyps ≥ 2cm.







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

TITLE PAGE

Cold versus Hot Snare Endoscopic Resection of Large Non-Pedunculated Colorectal Polyps

(Randomized-controlled German CHRONICLE-trial)

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ABBREVIATIONS

AE	Adverse event
APT	Antiplatelet therapy
ASA	American Society of Anesthesiologists classification
ASGE	American Society of Gastroenterology
BBPS	Boston Bowel Preparation Scale
CI	Confidence interval
cm	centimeter
CSPEB	Clinically significant postendoscopic bleeding
DOAC	Direct oral anticoagulants
DRKS	German Clinical Trials Registry
EFTR	Endoscopic full thickness resection
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
ESGE	European Society of Gastroenterology
FU	Follow-up
HGD	High grade dysplasia
HF	High frequency
ITT	Intention-to-treat
LGD	Low grade dysplasia
LST	Laterally spreading tumor
NICE	NBI International Colorectal Endoscopic classification
OR	Odds ratio
OTSC	Over-the-scope-clip
PP	Per protocol
RCT	Randomized controlled study
SSL	Sessile serrated lesion
TTSC	Through-the-scope-clip

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Ingo Steinbrück reports lecture fees and travel grants from Olympus and Falk Pharma.' Alanna Ebigbo reports lecture fees from Olympus Medical, FujiFilm, Pentax, Ambu, Falk Pharma and Medtronic. Armin Kuellmer reports lecture fees from Ovesco Endoscopy AG and Falk Pharma and consulting from KLS Martin Group, Tuttlingen, Germany. Arthur Schmidt reports research grants and lecture fees from Ovesco Endoscopy, consulting fees from KLS Martin and lecture fees from Falk Pharma and Olympus Medical. Markus Brand reports lecture fees from Abbvie, Takeda and Falk Pharma. Viktor Rempel reports lecture fees and travel grants from Olympus and lecture fees from Microtec. Andreas Wannhoff reports research grants from Fujifilm and Ovesco. Siegbert Faiss reports lecture fees and consulting fees from Olympus and Ovesco Endoscopy AG. Oliver Pech reports lecture fees from Medtronic, Aohua, AbbVie, Falk Pharma and Boston Scientific. Oliver Möschler reports lecture fees from Olympus Medical and FujiFilm. Franz Ludwig Dumoulin reports lecture fees and travel grants from Olympus. Thomas von Hahn reports lecture and consulting fees from Olympus Medical, grants/contracts and lecture fees from Puramatrix and lecture fees from Cook Medical and Falk Pharma. Hans-Dieter Allescher reports participation in advisory boards from Bayer and BMS and fiduciary role in DGVS and DGEBV. Stefan Gölder reports lecture fees from Astra Zeneca, Falk Pharma, Pfizer and Apollo Endosurgery. Martin Götz reports consulting fees from Abbvie, Janssen and Galapagos, member of advisory board of Boehringer Ingelheim and Alexion, lecture fees from Abbvie, Takeda, Pentax, MSD and DGVS. Alexander Meining reports consulting fees and patents from Ovesco Endoscopy AG, consulting fees from Olympus Medical and Pentax Medical, and lecture fees from Abbvie and Falk Pharma. Helmut Messmann reports consulting fees from Boston Scientific, CDx Diagnostics, Covidien, Erbe, Lumendi, Norgine, Olympus Medical, lecture fees from Covidien, Falk Pharma, Olympus Medical and travel grants from Amgen, Bayer, Falk Pharma, MSD, Novartis, Olympus medical and Roche. Thomas Rösch reports advisory fees for Olympus, lecture honoraria from Falk and Abbvie, and research support from Olympus, Erbe, Fujifilm, and Microtech. Hans-Peter Allgaier reports lecture fees and travel grants from Olympus. All other authors declare no competing interests.

CRediT AUTHORSHIP CONTRIBUTIONS

Dr Ingo Steinbrück (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Funding acquisition: Lead; Investigation: Equal; Methodology: Lead; Project administration: Equal; Resources: Equal; Software: Equal; Supervision: Equal; Validation: Equal; Visualization: Lead; Writing – original draft: Lead; Writing – review and editing: Lead). Dr Alanna Ebigbo (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Dr. Armin Kuellmer (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Prof. Dr. Arthur Schmidt (Conceptualization: Supporting; Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). PD Dr. Konstantinos Kouladouros (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Dr. Markus Brand (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Dr. Teresa Koenen (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Dr. Viktor Rempel (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). PD Dr. Andreas Wannhoff (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Prof. Siegbert Faiss (Conceptualization: Supporting; Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Prof. Oliver Pech (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Dr. Oliver Möschler (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Prof. Franz Ludwig Dumoulin (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Prof. Martha M. Kirstein (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Prof. Thomas von Hahn (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Prof. Hans-Dieter Allescher (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). PD Dr. Stefan Gölder (Data curation: Supporting; Investigation: Equal; Writing – review and editing: Equal). Prof. Martin Götz (Data

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DATA TRANSPARENCY STATEMENT

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 (e.g., for individual subgroups) together with other study groups.

DATA SHARING

All authors had access to the study data and reviewed and approved the final manuscript.

CLINICAL TRIAL REGISTRY WEBSITE: https://drks.de/search/de/trial/DRKS00025170

KEYWORDS

colonoscopy; endoscopic resection; endoscopic mucosal resection; cold snare; hot snare; adverse event; complication; residual adenoma

ABSTRACT

Background and aims: Endoscopic mucosal resection (EMR) is standard therapy for non-pedunculated colorectal polyps ≥20mm. Recently, it has been suggested that polyp resection without current (cold resection) may be superior to the standard technique using cutting/coagulation current (hot resection) by reducing adverse events (AE), but evidence from a randomized trial is missing.

Methods: In this randomized-controlled multicentric trial involving 19 centers, non-pedunculated colorectal polyps ≥20mm were randomly assigned to cold or hot EMR. Primary outcome was major AE (perforation or post-endoscopic bleeding). Among secondary outcomes major AE subcategories, postpolypectomy-syndrome and residual adenoma were most relevant.

Results: Between 2021 and 2023, 396 polyps in 363 patients (48.2% female) were enrolled for the intention-to-treat analysis. Major AE occurred in 1.0 % in the cold and in 7.9% in the hot group (p=0.001; Odds ratio [OR] 0.12 [95%-CI: 0.03-0.54]). Rates for perforation and post-endoscopic bleeding were significantly lower in the cold group with 0% vs. 3.9% (p=0.007) and 1.0% vs. 4.4% (p=0.040). Postpolypectomy-syndrome occurred with similar frequency (3.1% vs. 4.4%, p=0.490). After cold resection, residual adenoma was found more frequently, with 23.7% vs. 13.8% (p=0.020; OR 1.94 [95%-CI: 1.12-3.38]). In multivariable analysis, lesion diameter of ≥4cm was an independent predictor both for major AE (OR 3.37) and residual adenoma (OR 2.47), and high-grade dysplasia/cancer for residual adenoma (OR 2.92).

Conclusion: Cold resection of large non-pedunculated colorectal polyps appears considerably safer than hot EMR, however at the cost of a higher residual adenoma rate. Further studies have to confirm to which extent polyp size and histology can determine an individualized approach *(Trial number: DRKS00025170).*

INTRODUCTION

Endoscopic resection of adenomas during colonoscopy reduces colorectal cancer-related mortality [1]. While 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 ≥2cm, this is mostly achieved in two or more pieces, called piecemeal endoscopic mucosal resection (EMR) [2].

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

Another potentially easier and less costly option to reduce the rate of major AE is cold snare resection, which is already established for smaller polyps. Here, reduced bleeding rates have been reported, even in patients under 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 (RCT) can reliably help in decision making whether to use hot or cold snare resection for larger polyps. We therefore present the results of the first RCT comparing cold snare-EMR of non-pedunculated polyps ≥20mm with hot snare-EMR in a multicentric setting (The German CHRONICLE trial: **C**old vs. **h**ot snare **r**esection **o**f large **n**on-pedunculated polyps **i**n the **c**o**l**o**r**ectum).

MATERIAL AND METHODS

Study design

We conducted an investigator initiated, multicentric RCT with participation of 19 tertiary referral centers in Germany. 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 in the German Clinical Trials Registry (DRKS) before initiation (DRKS00025170). Data was collected prospectively at patient admission, during and after the procedure and during FU examinations. The article was written according to the CONSORT guideline.

Study population and Polyps

All patients, that were referred to the participating hospitals for resection of a large, colorectal polyp were screened for inclusion. Inclusion criteria were all colorectal non-pedunculated polyps ≥20mm. Exclusion criteria are provided in **suppl. Table S1** and were among others pedunculated or residual/recurrent polyps, suspected or histologically confirmed malignancy or polyps with nodules too large (>1-1.5cm) for the use of a cold snare. More than one polyp per patient could be included if

inclusion/exclusion criteria were fulfilled for each lesion. In these cases, major AE should be traced back to the individual polyp by information from repeated colonoscopy and/or surgery/CT.

1:1-randomization was done by the opening of opaque, sealed and numbered envelopes in the endoscopy room after confirmed eligibility by endoscopic evaluation (details in **suppl. Table S2**). 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 one eligible lesion a separate randomization was performed for each polyp in accordance with the randomization in previous related studies [10,26].

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 done more than 1000 colonoscopies and with prior experience in hot and cold snare resection of 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 [27]. Macroscopic polyp morphology was evaluated according to the classifications of Paris and Laterally spreading tumors (LST)/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 hot snare resection according to guideline recommendations [2,28]. A detailed description of the different treatment options in both groups is provided in **suppl. Table S3** and successful cold and hot snare resections are shown in **Figure 1** and **2**. As injectate usually normal saline was used, possibly with the addition of staining liquids (indigo carmine/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 (piecemeal technique). In both groups the 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, a straightening of the catheter or a jerky pull-maneuver was performed to ensure a successful resection. It was not allowed to utilize any hemostatic sprays or gels. In case of its use, of conversion to a different resection modality or the use of diathermy-based techniques in the cold-snare group the procedure was included in the intention-to-treat (ITT) but not in the per-protocol (PP) analysis. The treatment of AE was not standardized and was carried out at the discretion of the attending physicians.

Histological evaluation of the specimens was made by expert gastrointestinal pathologists in every participating center according to the valid guidelines [2,28].

After four weeks a standardized telephone interview was conducted to inquire about post-discharge complaints and/or AE. If the interview did not take place, it could be made up for during the first endoscopic FU, which occurred in 16/351 cases. The endoscopic FU was scheduled after four (+/- two) months, following the recommendations of the German guideline after piecemeal resection [28]. In case of residual/recurrent neoplasia an endoscopic resection should be undertaken. 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 in the participating hospitals and later transmitted to the study center on paper case report forms that were not changed after trial commencement.

Primary outcome parameter was the rate of major AE as a combined endpoint including any intra- or postprocedural perforation (=Sydney classification type 3-5 [29]) or post-endoscopic bleeding (=bleeding after completion of the procedure necessitating prolonged hospitalization, emergency department presentation and/or endoscopic, angiographic, or surgical intervention [17,27]). Self-limited clinical bleeding that did not result in patient presentation for medical assessment or was managed by observation on an outpatient basis was not included in this category. Similarly, postpolypectomy-syndrome was not included in this endpoint 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 (namely perforation and post-endoscopic bleeding), intra-procedural bleeding, postpolypectomy-syndrome, technical success (= 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 **suppl. Table S4**.

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 classification [30].

Sample size

The hypothesis of this study was that the resection of non-pedunculated colorectal polyps ≥2cm by cold snare-EMR is associated with a reduced major AE rate compared to hot resection. Estimated rates for major AE were 2.1% for cold snare- [27,31] and 8,2% for hot snare-EMR [32]. The difference of 6% was considered clinically relevant with a significant improvement in patient safety. To detect this difference with a power (1-β) of 80% and a significance level (α) of 5%, we calculated a sample size of 214 cases per group (including an estimated drop out-rate of 5%). The trial was stopped earlier according to pre-defined rules after a planned interim analysis, which was conducted after recruitment of the first 214 cases with available four-month-FU. The difference between the groups was 7.6% at that point, which was well above the original assumption and the rate of dropouts from ITT analysis was 7.9%. The re-calculated sample size based on these (also clinically significant) results, was 157 cases per group, a boundary that had already been crossed largely after 25 months of recruitment. Sample size calculation was performed by using Power and Sample Size.com Calculators (HyLown Consulting LLC™).

Statistical analysis

All statistical analyses were carried out using R (4.1.2) / R-Studio (2022.07.0) and were performed in the ITT and PP dataset. The ITT set included all randomized patients. The PP set excluded cases in which the allocated intervention was not carried out as planned (=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 two-sided χ^2- or Fisher´s exact test and were expressed as absolute and relative frequencies with 95%-confidence intervals (CI) and Odds ratios (OR). OR were corrected according to Haldane and Anscombe

in case of zero cell count. Continuous outcomes were compared using the Mann-Whitney U test and were presented as mean ±standard deviation/median (minimum-maximum value) and with 95%-CI. Missing values were reported but no imputation for missing data was performed. A p-value of <0.050 (2-sided) was considered statistically significant.

Uni- and multivariable analysis was performed to identify independent predictors for major AE and residual/recurrent adenoma/neoplasia. As possible predictors age, sex, ASA, anticoagulation, operators, low/middle/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. At first, an univariable logistic regression model (generalized linear model; rms package in R) was used and then a multivariable logistic regression model including those factors that were associated with the outcome of interest in the univariable analysis (p-value < 0.100).

A scheduled close-out monitoring was carried out by an independent monitoring committee after termination of recruitment and four-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 study design, data collection, analysis and interpretation, or writing of the report.

RESULTS

Baseline Data and Clinical characteristics

Between June 7, 2021, and July 17, 2023, 401 eligible polyps in 368 patients were identified for the study (**Figure 3**). Characteristics and performance of the participating centers are provided in **suppl. Table S5**. Five polyps (1.2%) were excluded during the procedure as they did not meet the inclusion criteria (pretreated lesions in three and pedunculated polyps in two cases). As shown in **Table 1**, a total of 396 polyps in 363 patients (188 [51.8%] male and 175 [48.2%] female, mean age 65.87 [±10.50] years) were randomized and enrolled for the ITT analysis. 82 participants (22.6%) received antiplatelet/anticoagulant therapy (for details **suppl. Table S6**) with a significantly higher rate in the hot snare group (19.0% vs. 28.1%, p=0.038). The greater diameter of the lesions was 3.01 (±1.02; 2.0-8.0) cm on average. 69.2% of the lesions were in the cecum and ascending colon. Morphologic assessment revealed LST granular-type homogenous in 31.8% and suspected SSL in 25.0%. After histologic evaluation, 35.4% were in fact SSL/hyperplastic and 45.7% adenomas with low grade dysplasia (**Table 1**, further histologic details in **suppl. Table S7**).

370 polyps were eligible for PP analysis (**Figure 3**). Reasons for non-eligibility were conversion in 20 cases (15 [7.8%] in the cold and five [2.5%] in the hot group) and violation of the study protocol in six cases (five [2.6%] in the cold and one [0.5%] in the hot group). Cold resection was converted to hot in 14 cases and to Endoscopic full thickness resection (EFTR) in one case. The hot snare was converted to EFTR in three cases and to Endoscopic submucosal dissection (ESD) and cold resection in one case each (**suppl. Table S8**). As the reason for conversion, technical difficulties were stated in all cases. For patient and lesion details in the PP dataset see **suppl. Table S9**.

The technical success rate was 92.2% (178/193; 95%-CI: 87.5-95.3%) in the cold and 97.5% (198/203; 95%-CI: 94.4-98.9%) in the hot group (p=0.022, OR 0.30 [95% CI: 0.11-0.84]). There was no significant difference in resection speed with 22.59 (±16.68; 95%-CI: 20.19-24.98) vs. 21.72 (± 19.22; 95%-CI: 19.04-24.40) cm^2/h (p=0.281). Technical data including the used snares are summarized in **suppl. Table S10**. Submucosal injection was performed in 73.1% in the cold and in 95.1% in the hot group (p<0.001),

rates of en bloc resection were 2.1% and 8.4% (p<0.001). The majority of cold snares were smaller than the hot snares with significantly more resections in more than five pieces (68.9% vs. 45.8% [p<0.001]), respectively. Prophylactic clipping was performed in 18.7% in the cold and in 37.4% in the hot group (p<0.001), clip-closure of the resection site in 13.5% and 28.1% (p<0.001), prophylactic coagulation of blood vessels in 0.5% and 17.7% (p<0.001) and coagulation of the entire margin in 1.6% and 30.5% (p<0.001), respectively.

The results of the ITT analysis for the most relevant outcome parameters were as follows:

Primary outcome

The rates of major AE were 1.0% (2/193; 95%-CI: 0.2-3.7%) in the cold and 7.9% (16/203; 95%-CI: 4.9-12.4%) in the hot-EMR group (p=0.001; OR 0.12 [95%-CI: 0.03-0.54]) in the per-polyp analysis (**Table 2**). The per-patient analysis yielded analogous results (**suppl. Table S11**). All major AEs were clearly attributable to a single polyp. Only one major AE occurred in a patient with more than one resected polyp, which was an interprocedurally diagnosed and treated perforation.

Secondary outcomes – AE/events

The results of the per-polyp analysis for the major AE subcategories are presented in **Table 2** and **suppl. Table S12**. Perforation rates were 0% (0/193; 95%-CI: 0.0-1.8%) in the cold and 3.9% (8/203; 95%-CI: 2.0-7.6%) in the hot EMR-group (p=0.007; OR 0.06 [95%-CI: 0.003-1.04]). All perforations were located in the right colon and occurred intraprocedurally in seven cases and within 24 hours in one case. Previous lesion assessment was LST granular type in five and SSL in three cases with diameters between 2.5 and 6.0cm. Five perforations were type 3 and three type 4 according to the Sydney classification. All intraprocedural perforations were successfully treated endoscopically by clipping and the delayed perforation by in-patient monitoring and antibiotic therapy. In one case, both a perforation and a post-procedural bleeding occurred. Rates of post-procedural bleeding were 1.0% (2/193; 95%-CI: 0.2-3.7%) in the cold and 4.4% (9/203; 95%-CI: 2.3-8.2%) in the hot EMR-group (p=0.040; OR 0.23 [95%-CI: 0.05-1.06]). Successful endoscopic treatment was performed in nine and prolonged in-patient monitoring in two cases. Other AE/events are provided in **Table 2** and **suppl. Table S13**. Significant differences in favor of cold resection were found in intraprocedural bleedings. The rates of postpolypectomy-syndromes were not significantly different with 6/193 (3.1%) in the cold and 9/203 (4.4%) in the hot group (p=0.490). No patient received surgical therapy due to AE and no treatment-related deaths were observed. The per-patient analysis yielded analogous results (**suppl. Table S11**).

Secondary outcomes - residual/recurrent neoplasia at the first FU examination

Data regarding residual adenoma/neoplasia was available in 351 cases (88.6%), namely in 346 endoscopic FU and in five specimens after surgical resection. Reasons for surgery were histology of adenocarcinoma (two cases in the cold and three cases in the hot group). Mean FU period was 4.35 (±2.14; 1-17) months. In the ITT dataset, the rate of recurrent/residual neoplasia was 23.7% (42/177; 95%-CI: 18.1-30.5%) after cold and 13.8% (24/174; 95%-CI: 9.4-19.7%) after hot EMR (p=0.020, 1.94 [95%-CI: 1.12-3.38]) (**Table 2,** for the per-patient analysis **suppl. Table S11**). In 9/66 cases (13.6%) residual neoplasia was diagnosed histologically from biopsies of inconspicuous scars. 96.8% of the endoscopically diagnosed residual lesions were re-treated by endoscopic resection. Two cases from the initial cold snare group received surgical treatment due to malignant histology in the specimen from the FU examination (for details **suppl. Table S14**).

For residual/recurrent neoplasia a post-hoc subgroup analysis according to morphological criteria (SSL/LST-classification) was done (**Table 3**). For suspected SSL the rate of residual neoplasia was 8.3% (4/48; 95%-CI: 3.3-19.5%) in the cold and 4.8% (2/42; 95%-CI: 1.3-15.8%) in the hot EMR-group (p=0.681). However, the macroscopic assessment of SSL/hyperplastic polyps was confirmed by histopathology in only 81.8%, and only 70.7% of the histopathologically diagnosed SSL were previously correctly classified by the examiner. For the LST only the nodular-mixed types had significantly different rates of residual adenoma with 40.5% (15/37; 95%-CI: 26.3-56.5%) in the cold and 14.3% (6/42; 95%-CI: 6.7-27.8%) in the hot group (p=0.011; OR 3.97 [95%-CI: 1.38-12.80]). But it must be added that after histopathological examination of the LST non-granular type 28.9% were in fact SSL/hyperplastic and only 4.8% malignant.

The results in the PP datasets were similar to the ITT analyses (see **Table 2**, **Table 3** and **suppl. Table S11**).

Predictors for major AE and residual/recurrent neoplasia

The only independent predictor for major AE in uni-/multivariable regression analysis was a polyp diameter ≥4cm (OR 3.37 [95%-CI: 1.25-9.09]) (**suppl. Table S15**). Independent predictors for residual/recurrent neoplasia in uni-/multivariable regression analysis were polyp diameter ≥4cm (OR 2.47 [95%-CI: 1.21-5.03]) and histology of adenoma with high grade dysplasia/carcinoma (OR 2.92 [95%-CI: 1.22-7.00]) (**suppl. Table S16**).

DISCUSSION

To our knowledge, this is the first RCT comparing cold and hot snare resection of non-pedunculated colorectal polyps ≥20mm. 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 AE after hot-EMR of polyps ≥2cm were summarized in a review of the ASGE with perforation rates of 0.1-2.2% (pooled rate 1.1%), and post-endoscopic bleedings of 0.2-8.4% (pooled rate 3.7%) [14]. This data is concordant to our major AE rate of 7.9%. Such complications require additional interventions and often patient re-admission, or prolongation of hospital stay [33]. This makes measures to avoid major AE and associated sequelae and costs worthwhile, especially since out-patient performance of EMR is standard in some countries and will be increasingly mandated in others.

Cold snare resection is a promising technique to make EMR safer. The superiority of the cold snare in terms of post-procedural bleeding was initially shown for polyps <10mm [34,35] and recently also for lesions of 10-20mm [36]. In larger flat polyps (≥20mm), studies mostly included SSL, and again, complication rates were lower compared to hot EMR [22,31]. Post-procedural bleeding rates varied between 0% and 3.8% and perforations were close to zero in all trials and meta-analyses. The same was reported from a retrospective observational study in the duodenum [37].

These results are confirmed by our RCT both in ITT and PP analyses, with a reduction of major AE by more than 85%, namely from 7.9% to 1.0%. This difference was even higher than originally assumed, so that the recruitment could be terminated prematurely. No perforations occurred with cold EMR. The difference to the eight 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 non-surgical treatment of all cases confirms the results of a retrospective

cohort study, in which surgery was not necessary in the majority of interventional perforations [33]. This has to be considered when the severity of perforations is assessed. Also, post-endoscopic 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 AE. It has been shown that prophylactic clip-closure of the resection area after piecemeal-EMR also reduces post-endoscopic 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 AE. However, disadvantages of this technique are the time and cost involved and the technical difficulty to close 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=0.003), namely 8/193 (4.1%) vs. 25/203 (12.3%). These results make cold snare resection particularly interesting for out-patient management of large flat polyps. The only independent predictor for major AE in uni-/multivariable regression analysis was a polyp diameter ≥4cm, which has already been demonstrated before for hot snare-EMR [32]. 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 (51µm vs. 933µm), which might also contribute to the lower risk of delayed bleeding [38]. It has been shown that also histologic damage of submucosal arteries is reduced from 39% to 22% with a significantly lower post-procedural bleeding rate compared to hot resection [21]. Whether vessel defect closure mechanisms after cold rupture may function better than cutting with current can only be speculated about.

Regarding minor AE, 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 [39]. 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 [40] 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. Also, 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 to a meta-analysis of small polyp resections, where rates of intraprocedural bleeding were higher for the cold snare in comparison to standard therapy with 6.6% vs. 3.3%, perhaps again due to definition and other methodological issues [41].

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 one series of 204 polyps ≥2cm, the rate of residual neoplasia was only 5.5%, but 2/3 of polyps were SSL [27]. In another study with 310 large polyps, the rate was 34% with only 20% being SSL/hyperplastic [42]. Finally, a smaller series of flat polyps ≥1cm (n=73) with 80% adenomas had a rate of residual adenoma of 9.7%. 51% of these lesions were ≥2cm, and all cases (n=7) occurred only in this group. This resulted in a residual adenoma rate of 25% in this very small subgroup [43]. This retrospective data suggests 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 [37] but was substantial in two other trials [44,45].

The higher rate of residual adenoma/neoplasia after cold EMR of flat colorectal polyps ≥2cm was confirmed by our RCT with an increase of 10% compared to 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 [46]. 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% [47]. One limitation of our study is the not systematically performed margin coagulation. This has recently been shown to reduce residual/recurrent neoplasia to less than 5-10% [8,9,47-51]. 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 [2,28] 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 no independent predictive factor for residual/recurrent neoplasia in uni-/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. On the other hand, our rate of residual adenoma after cold snare resection is similar to previous German reports of hot snare-EMR without margin coagulation [4,40]. 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. On the other hand, frequent colonoscopies should be avoided since patient adherence may be variable and limited. If below a certain rate of residual adenoma a systematic early FU is expendable, is a matter of discussion as many database studies show that advanced adenomas still have a worse prognosis regarding interval cancers [52,53]. Also, the recurrence rate could still be underrated in our study as the median FU interval was 4.35 (±2.14) months, which is below six months as the optimal interval for the detection of residual adenoma [46]. 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 [54,55]. Irrespectively, improvements of cold-EMR are indicated to make it more effective. Technical modifications of the cold/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 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 SSL seem to be best suited for cold snare resection, since recurrence rates were similar in both groups. This is in concordance with previous retrospective series [22,37], 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/carcinoma and polyp diameter ≥4cm were independent predictors for residual neoplasia. Thus, another practical conclusion may be that lesions of larger size and those with a complex morphology should further be treated by hot snare-EMR with additional measures.

Also pre-interventional optical assessment of polyps needs improval according to our data with a high number of false-positive and -negative SSL-estimations. Imaging studies involving dedicated experts usually reach better results. But (possibly more representative) real-life data suggest a lower accuracy

[56]. 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 AE and the reliable detection of residual adenoma by taking biopsies also 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 [2,28] 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 to blind 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 (size, LST-classification) are prone to errors, a problem which we share with almost all other publications on this topic. Both might lower the generalizability of the results.

In summary, the results of our RCT indicate that cold resection of large non-pedunculated 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 outcome and cost-effectiveness of polypectomy (for example by combining the safety of the cold snare with measures to reduce recurrence) and which allocation strategies to the different resection methods are the most effective ones.

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TABLES

Table 1: Patient and lesion characteristics (intention-to-treat dataset)

	All 396 polyps (363 patients)	Cold snare-EMR 193 polyps (184 patients)	Hot snare-EMR 203 polyps (192 patients)	p-value
Patient age	65.87 (±10.50; 21-92)	65.11 (±11.04; 21-92)	66.34 (±10.36; 21-86)	0.286[c]
Patient sex				
male	188/363 (51.8%)	90/184 (48.9%)	107/192 (55.7%)	0.186[a]
female	175/363 (48.2%)	94/184 (51.1%)	85/192 (44.3%)	
Patient ASA grade	1.68 (±0.59; 1-3)	1.68 (±0.61; 1-3)	1.69 (±0.57; 1-3)	0.801[c]
I	139/363 (38.3%)	72/184 (39.1%)	70/192 (36.5%)	
II	200/363 (55.1%)	98/184 (53.3%)	111/192 (57.8%)	0.598[a]
III	24/363 (6.6%)	14/184 (7.6%)	11/192 (5.7%)	
Antiplatelet-/Anticoagulant therapy	82/363 (22.6%)	35/184 (19.0%)	54/192 (28.1%)	**0.038**[a]
Bowel cleaning score (BBPS)	7.44 (±1.54; 4-9)	7.38 (±1.54; 4-9)	7.47 (±1.53; 4-9)	0.539[c]
Greater lesion diameter (cm)	3.01 (±1.02; 2.0-8.0)	3.05 (±1.07; 2.0-7.0)	2.98 (±0.98; 2.0-8.0)	0.803[c]
Lesion size (cm^2)	5.81 (±4.37; 0.79-28.27)	6.02 (±4.73; 0.79-27.49)	5.60 (±4.00; 1.18-28.27)	0.805[c]
Lesion localization				
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%)	0.794[a]
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				
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%)	0.933[b]
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				
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%)	0.937[a]
non-granular type flat elevated	73/396 (18.4%)	34/193 (17.6%)	39/203 (19.2%)	
non-granular type pseudodepressed	10/396 (2.5%)	5/193 (2.6%)	5/203 (2.5%)	
Suspected sessile serrated lesion	99/396 (25.0%)	52/193 (26.9%)	47/203 (23.2%)	
Histology				
SSL/hyperplastic polyps	140/396 (35.4%)	76/193 (39.4%)	64/203 (31.5%)	
Adenoma LGD	181/396 (45.7%)	80/193 (41.5%)	101/203 (49.8%)	0.358[b]
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%)	0.892[a]
Adenoma with villous components	102/396 (25.8%)	47/193 (24.4%)	55/203 (27.1%)	

ASA: American Society of Anesthesiologists classification, BBPS: Boston Bowel Preparation Scale, NICE: NBI International Colorectal Endoscopic classification, JNET: Japanese NBI expert Team classification, SSL: sessile serrated lesion, LGD: low grade dysplasia, HGD: high grade dysplasia, [a]: Chi-square test, [b]: Fisher´s exact test, [c]: Wilcoxon-Mann-Whitney U test.

Table 2: Outcomes in the intention-to-treat and per-protocol analysis

	Cold snare-EMR	Hot snare-EMR	p	Odds ratio [95%-CI]
	ITT (n=193)	ITT (n=203)		
	Value [95%-CI]	Value [95%-CI]		
Major AE	2 (1.0%) [0.2-3.7%]	16 (7.9%) [4.9-12.4%]	**0.001**[a]	**0.12** [0.03- 0.54]
Perforation	0 [0.0-1.8%]	8 (3.9%) [2.0-7.6%]	**0.007**[b]	**0.06** [0.003 - 1.04]
Post-procedural bleeding	2 (1.0%) [0.2-3.7%]	9 (4.4%) [2.3-8.2%]	**0.040**[a]	**0.23** [0.05- 1.06]
Intra-procedural bleeding	27 (14.0%) [9.8-19.5%]	46 (22.7%) [17.4-28.8%]	**0.026**[a]	**0.56** [0.33- 0.94]
Postpolypectomy-syndrome	6 (3.1%) [1.4-6.6%]	9 (4.4%) [2.3-8.2%]	0.490[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%]	**0.020**[b]	**1.94** [1.12- 3.38]
	PP (n=173)	**PP (n=197)**	**P**	**Odds ratio [95%-CI]**
	Value [95%-CI]	**Value [95%-CI]**		
Major AE	2 (1.2%) [0.3-4.1%]	15 (7.6%) [4.6-12.1%]	**0.003**[a]	**0.14** [0.03-0.63]
Perforation	0 [0.0-2.1%]	8 (4.1%) [2.1-7.8%]	**0.008**[b]	**0.06** [0.004 - 1.12]
Post-procedural bleeding	2 (1.2%) [0.3-4.1%]	8 (4.1%) [2.1-7.8%]	0.112[a]	0.28 [0.06-1.32]
Intra-procedural bleeding	18 (10.4%) [6.7-15.8%]	44 (22.3%) [17.1-28.6%]	**0.002**[a]	**0.40** [0.22-0.73]
Postpolypectomy-syndrome	6 (3.5%) [1.6-7.4%]	9 (4.6%) [2.4-8.5%]	0.592[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%]	**0.006**[b]	**2.30** [1.28-4.17]

ITT: Intention-to-treat analysis, PP: Per-protocol analysis, AE: Adverse event, FU: Follow up, CI: Confidence interval, [a]:Chi-square test, [b]: Fisher´s exact test.

Table 3: Subgroup analysis for residual/recurrent adenoma/neoplasia at the first FU examination (intention-to-treat and per-protocol datasets)

Subgroup	Cold snare-EMR	Hot snare-EMR	p	Odds ratio [95%-CI]
	ITT	ITT		
	Value [95%-CI]	Value [95%-CI]		
Suspected SSL	4/48 (8.3%) [3.3-19.5%]	2/42 (4.8%) [1.3-15.8%]	0.681[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%]	0.116[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%]	**0.011**[a]	**3.97** [1.38-12.80]
LST non-granular type	6/35 (17.1%) [8.1-32.7%]	4/33 (12.1%) [4.8-27.3%]	0.735[b]	1.48 [0.37-6.56]
Subgroup	**PP**	**PP**	**P**	**Odds ratio [95%-CI]**
	Value [95%-CI]	**Value [95%-CI]**		
Suspected SSL	4/44 (9.1%) [3.6-21.2%]	2/41 (4.9%) [1.3-16.1%]	0.677[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%]	0.261[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%]	**0.007**[a]	**4.74** [1.52-17.09]
LST non-granular type	6/33 (18.2%) [8.6-34.4%]	2/30 (6.7%) [1.8-21.3%]	0.261[b]	2.93 [0.59-23.67]

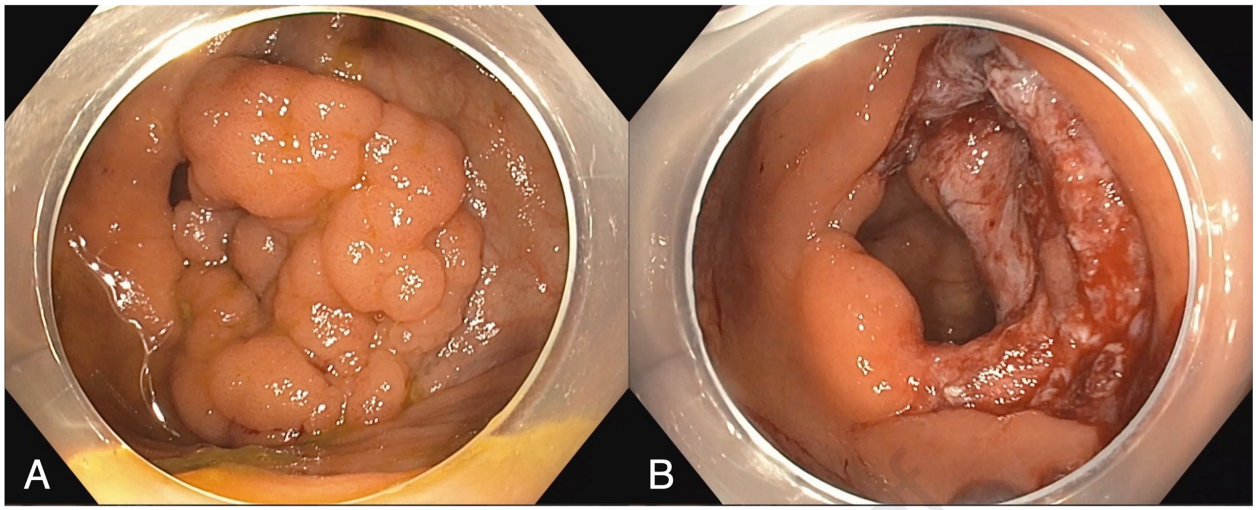
ITT: Intention-to-treat analysis, PP: Per-protocol analysis, SSL: sessile serrated lesion, LST: Laterally spreading tumor, neopl.: neoplasia; Frequ.: frequency, CI: confidence interval, [a]: Chi-square test, [b]: Fisher´s exact test.

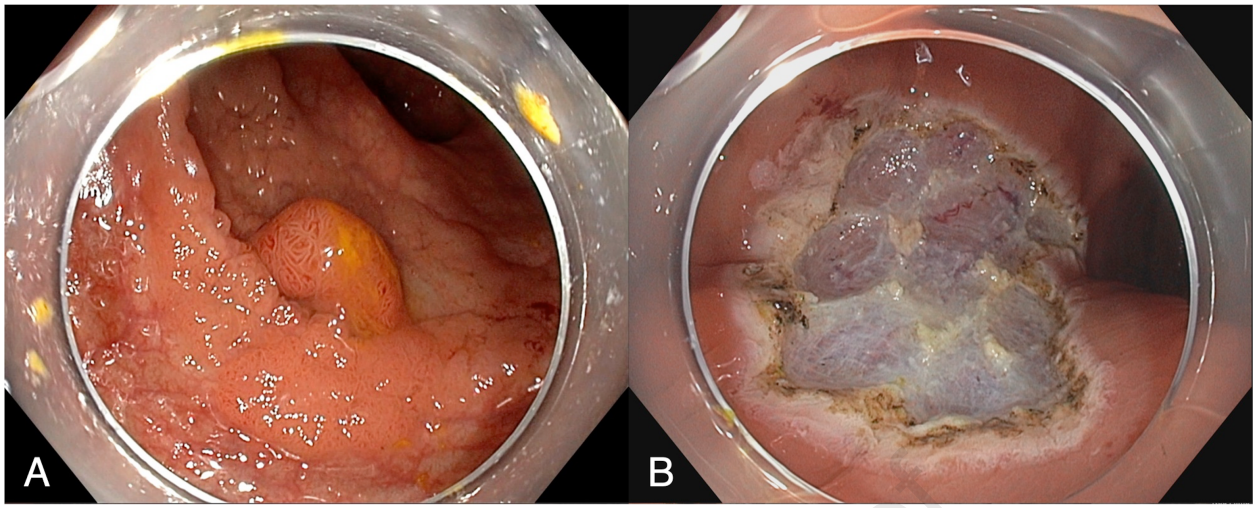
FIGURES

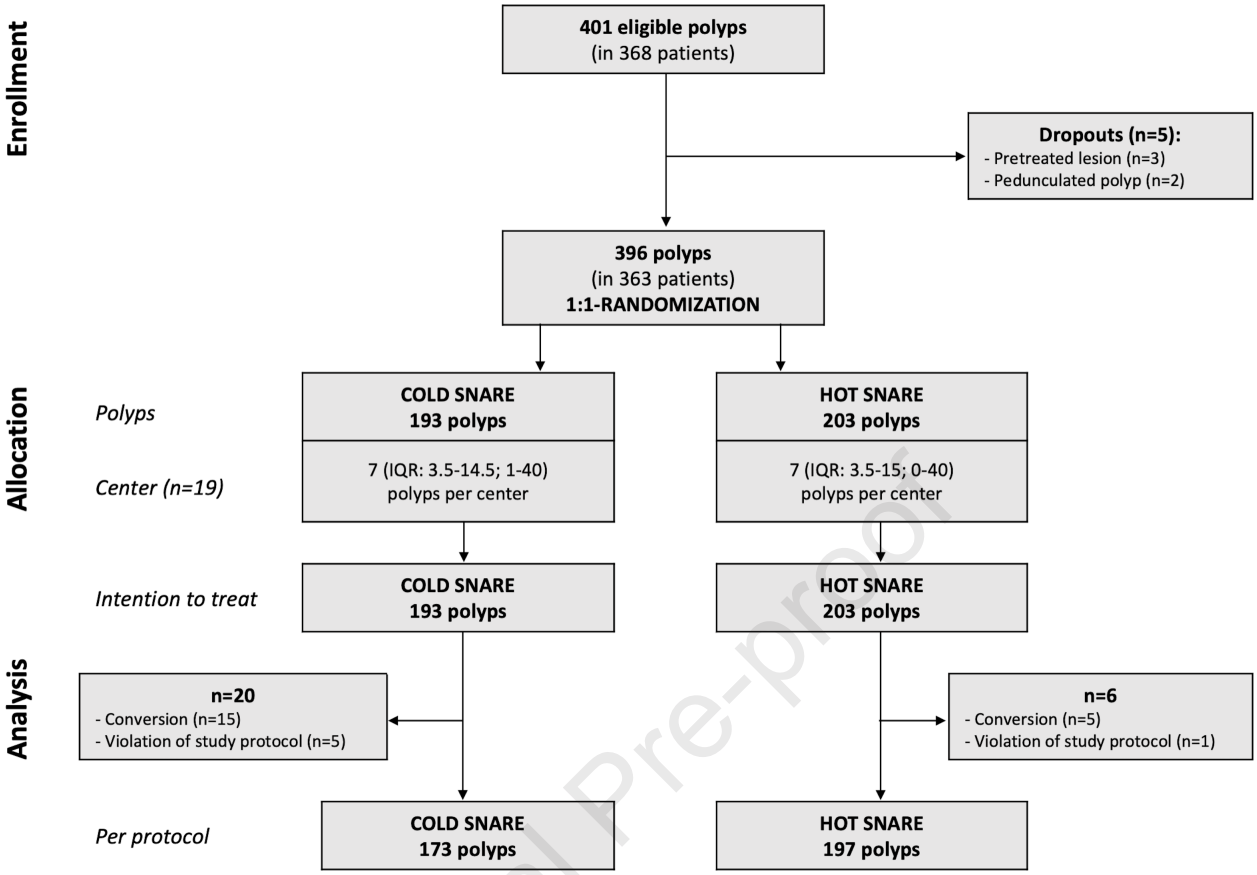
Figure 1: Laterally spreading tumor nodular-mixed type in the ascending colon before (A) and after (B) cold snare piecemeal-EMR

Figure 2: Laterally spreading tumor nodular-mixed type in the ascending colon before (A) and after (B) hot snare piecemeal-EMR with margin coagulation

Figure 3: Trial flow-sheet







SUPPLEMENTARY TABLES

Suppl. Table S1: Exclusion criteria

- Pedunculated polyp
- Residual/recurrent polyps after prior endoscopic treatment
- Endoscopic suspicion of malignancy (JNET type III/NICE 3-pattern)
- Histologically confirmed malignancy
- Polyps with nodules too large (>1-1.5cm) for the use of a cold snare
- Age <18 years
- Incapability or unwillingness of giving informed consent
- Pregnancy
- Coagulation disorders
- Chronic inflammatory bowel disease
- Patient status grade IV or V according to the American Society of Anesthesiologists (ASA)
- Poor bowel preparation (grade 0-3 in the Boston Bowel Preparation Scale [BBPS])
- Antiplatelet/anticoagulant medication that could not be paused as recommended in the current guideline [25]:
    - **Acetylsalicylic acid (ASA):** from 5 days before until 2 days after the intervention (in case of low thromboembolc risk), otherwise continuous administration
    - **ASA+ Adenosine-diphosphate (ADP) receptor antagonist:** from 5 days before until 2 days after the intervention
    - **Direct oral anticoagulation (DOAC):** at least one day before until one day after the intervention (depending on the half-life)
    - **Marcumar:** from at least 7 days before until 1 day after the intervention (bridging with heparin)
    - **Heparin (therapeutic treatment):** from at least one day before until 6 hours after the intervention
    - **Heparin (prophylactic treatment):** from at least 12 hours before until 6 hours after the intervention

Suppl. Table S2: Description of the randomization process

Every center had received a package of 30 opaque, sealed and numbered envelopes containing 15 letters each, assigning to the cold snare- or hot snare-treatment group in random order. The envelopes were opened by numbers for 1:1-randomization. After inclusion of 30 cases, the center received a new package from the study center. If a polyp was found to be eligible for randomization by the examiner after endoscopic evaluation, the envelope was opened in the endoscopy room before the start of the resection by a research assistant that was not otherwise involved in the study.

Suppl. Table S3: Details of treatment in the study group and in the control arm

Cold snare-treatment group (study group)	Hot snare-treatment group (control group using standard therapy [2,28])
- Use of a snare approved for cold snare resection (thin-wire) cold snare or hybrid snare without current)	- Use of a snare approved for hot snare resection with a high frequency (HF) diathermy device device (e.g. Erbe VIO 200D™/300D™/3™, Olympus ESG-100™/ 300™ or similar)
- Submucosal injection prior to and subsequently during the resection*	- Submucosal injection prior to and subsequently during the resection*
- Additional resections with cold biopsy forceps*	- Additional resection with cold or hot biopsy forceps (avulsion) and/or coagulation of remnant adenoma*
- Treatment of intraprocedural bleeding with injection and/or hemoclips	- Treatment of intraprocedural bleeding with injections, hemoclips and/or coagulation
- Treatment of perforation with hemoclips or Over-the-scope-clips	- Treatment of perforation with hemoclips or Over-the-scope-clips
- Prevention of delayed bleeding by clipping of visible vessels or of the entire resection site*	- Prevention of delayed bleeding by clipping of visible vessels or of the entire resection site*
- No coagulation of the resection margin	- Coagulation of resection margin*
- No use of any devices with current, hemostatic sprays or gels for treatment or prevention of bleeding	- No use of hemostatic sprays or gels for treatment or prevention of bleeding

*Optional.

Suppl. Table S4: Secondary outcomes and other variables

Secondary outcomes:

- Perforation (Sydney classification type 3-5)
- Post-endoscopic bleeding (bleeding after completion of the procedure necessitating prolonged hospitalization, emergency department presentation and/or endoscopic, angiographic, or surgical intervention)
- Intra-procedural bleeding (bleeding >60 seconds that requires endoscopic intervention)
- Postpolypectomy-syndrome (localized abdominal pain within 24 hours after the procedure with successful treatment by observation, analgetics and/or antibiotics)
- Technical success of the initial resection technique (successful removal of the lesion without conversion to another resection technique)
- Resection speed (=lesion size (cm^2)/duration of procedure (hours))
- Residual/recurrent adenoma or neoplasia (assessed at the first FU endoscopy (including routine biopsies of normal looking scars) or in case of surgery in the surgical preparation)

Other documented variables:

- Recruitment in the study centers (low volume (=1 per month), middle volume (=2 per month), high volume (≥3 per month))
- Size (two maximum diameters)
- Colorectal localization
- Morphology (Laterally spreading tumor (LST) and Paris classification)
- Use and composition of injectate
- Used snare(s) (company/size/number)
- Reason for snare exchange
- Therapy of intra-/postprocedural adverse events
- Number of specimens (en bloc, 1-5, >5)
- Rates and types of additional therapy
- Prophylactic additional interventions
- Clipping of vessels (as treatment of intra-procedural bleeding or prophylactic)
- Clip-closure of the resection site (as treatment of intra-procedural bleeding or prophylactic)
- Duration of procedure (=advancement of the first device (cold snare)/preparation of the high frequency generator (hot snare) until the end of resection (including complication management and prophylactic measures) in minutes
- Level of difficulty (1-3= easy/middle/difficult)
- In case of a difficult procedure reason
- In case of technical failure alternative therapy
- In case of adverse events time and treatment
- Histologies
- In case of residual neoplasia during endoscopic follow-up resection technique

Suppl. Table S5: Characteristics and performance of the participating centers

	Number of cases	Time of recruitment (months)	Number of operators
Ev. Diakoniekrankenhaus Freiburg	81	25	5
University Hospital Augsburg	46	20	3
University Hospital Freiburg	38	24	3
University Hospital Mannheim	34	21	3
University Hospital Würzburg	33	21	2
Rhein-Maas-Klinikum Würselen	28	21	2
St. Anna Hospital Herne	27	22	5
RKH Klinikum Ludwigsburg	15	5	2
Sana Klinikum Lichtenberg	14	17	3
Krankenhaus Barmherzige Brüder Regensburg	14	21	3
Marienhospital Osnabrück	14	21	1
Gemeinschaftskrankenhaus Bonn	13	18	2
University Hospital Lübeck	12	18	2
Asklepios Clinic Barmbek	10	22	2
Klinikum Garmisch-Patenkirchen	9	17	1
Ostalb-Klinikum Aalen	4	13	2
Klinikum Sindelfingen-Böblingen	4	14	1
Allgemeines Krankenhaus Celle	4	20	2
Klinikum Traunstein	1	4	1

Suppl. Table S6: Anticoagulation treatment in both groups

	Cold snare-EMR 184 patients	**Hot snare-EMR** 192 patients
APT	18 (9.8%)	33 (17.2%)
Dual APT	0	1 (0.5%)
DOAC/Marcumar	16 (8.7%)	18 (9.4%)
APT+DOAC	1 (0.5%)	2 (1.0%)

APT: Antiplatelet therapy, DOAC: Direct oral anticoagulants.

Suppl. Table S7: Detailed polyp histology in both groups (intention-to-treat dataset)

	All **396 polyps**	**Cold snare-EMR** **193 polyps**	**Hot snare-EMR** **203 polyps**
Sessile serrated lesion	131 (33.1%)	67 (34.7%)	64 (31.5%)
Sessile serrated lesion HGD	2 (0.5%)	2 (1.0%)	0
Hyperplastic polyp	7 (1.8%)	7 (3.6%)	0
Tubular adenoma LGD	113 (28.5%)	48 (24.9%)	65 (32.0%)
Tubular adenoma HGD	28 (7.1%)	16 (8.3%)	12 (5.9%)
Tubulovillous adenoma LGD	58 (14.6%)	29 (15.0%)	29 (14.3%)
Tubulovillous adenoma HGD	34 (8.6%)	12 (6.2%)	22 (10.8%)
Villous adenoma LGD	3 (0.8%)	1 (0.5%)	2 (1.0%)
Villous adenoma HGD	4 1.0%)	4 (2.1%)	0
Mixed polyp LGD	7 (1.8%)	2 (1.0%)	5 (2.5%)
Mixed polyp HGD	1 (0.3%)	1 (0.5%)	0
Adenocarcinoma	8 (2.0%)	4 (2.1%)	4 (2.0%)

EMR: Endoscopic mucosal resection, SSL: sessile serrated lesion, HGD: high grade dysplasia, LGD: low grade dysplasia.

Suppl. Table S8: Reasons for non-eligibility for the per-protocol analysis

	Cold snare-EMR 193 polyps	Hot snare-EMR 203 polyps
Not eligible for PP analysis	20 (10.4%)	6 (3.0%)
Conversion	15 (7.8%)	5 (2.5%)
To cold snare/hot snare	14	1
To Endoscopic full thickness resection	1	3
To ESD + Argonplasmacoagulation	0	1
Violation of study protocol	5 (2.6%)	1 (0.5%)
Therapeutic use of hemostatic gel/powder	2	0
Prophylactic use of hemostatic gel/powder	1	1
Use of electrocoagulation (cold snare group)	2	0

EMR: Endoscopic mucosal resection, ESD: Endoscopic submucosal dissection.

Suppl. Table S9: Patient and lesion characteristics (per-protocol dataset)

	Cold snare-EMR 173 polyps (165 patients)	Hot snare-EMR 197 polyps (186 patients)	p-value
Patient age	64.96 (±11.19; 21-92)	66.27 (±10.43; 21-86)	0.274[c]
Patient sex			
male	79/165 (47.9%)	102/186 (54.8%)	0.193[a]
female	86/165 (52.1%)	84/186 (45.2%)	
Patient ASA grade	1.67 (±0.62; 1-3)	1.69 (±0.58; 1-3)	0.566[c]
I	68/165 (41.2%)	68/186 (36.6%)	
II	84/165 (50.9%)	107/186 (57.5%)	0.430[a]
III	13/165 (7.9%)	11/186 (5.9%)	
Antiplatelet-/Anticoagulant therapy	32/165 (19.4%)	52/186 (28.0%)	0.061[a]
Bowel cleaning score (BBPS)	7.37 (±1.53; 4-9)	7.48 (±1.51; 4-9)	0.475[c]
Greater lesion diameter (cm)	3.01 (±1.07; 2.0-7.0)	2.95 (±0.95; 2.0-8.0)	0.858[c]
Lesion size (cm^2)	5.84 (±4.73; 0.79-27.49)	5.50 (±3.87; 1.18-28.27)	0.549[c]
Lesion localization			
Cecum	49/173 (28.3%)	52/197 (26.4%)	
Ascending colon	72/173 (41.6%)	86/197 (43.7%)	
Transverse colon	34/173 (19.7%)	32/197 (16.2%)	0.779[b]
Descending colon	10/173 (5.8%)	12/197 (6.1%)	
Sigmoid colon	6/173 (3.5%)	9/197 (4.6%)	
Rectum	2/173 (1.2%)	6/197 (3.0%)	
Paris classification			
0-Is	15/173 (8.7%)	16/197 (8.1%)	
0-IIa	134/173 (77.5%)	154/197 (78.2%)	
0-IIb	2/173 (1.2%)	2/197 (1.0%)	
0-Is+IIa	16/173 (9.2%)	16/197 (8.1%)	0.914[b]
0-IIa+Is	4/173 (2.3%)	8/197 (4.1%)	
0-IIa+Ic	0	0	
0-IIc+IIa	0	0	
0-IIa+IIc	2/173 (1.2%)	1/197 (0.5%)	
Laterally spreading tumor			
granular type homogenous	54/173 (31.2%)	65/197 (33.0%)	
granular type nodular-mixed	36/173 (20.8%)	45/197 (22.8%)	0.911[b]
non-granular type flat elevated	32/173 (18.5%)	37/197 (18.8%)	
non-granular type pseudodepressed	3/173 (1.7%)	4/197 (2.0%)	
Suspected sessile serrated lesion	48/173 (27.7%)	46/197 (23.4%)	
Histology			
SSL/hyperplastic polyps	74/173 (42.8%)	62/197 (31.5%)	
Adenoma LGD	71/173 (41.0%)	100/197 (50.8%)	0.148[b]
Adenoma HGD	26/173 (15.0%)	32/197 (16.2%)	
Adenocarcinoma in adenoma	2/173 (1.2%)	3/197 (1.5%)	
Tubular adenoma	59/173 (34.1%)	78/197 (39.6%)	0.791[a]
Adenoma with villous components	38/173 (22.0%)	54/197 (27.4%)	

ASA: American Society of Anesthesiologists classification, BBPS: Boston Bowel Preparation Scale, NICE: NBI International Colorectal Endoscopic classification, JNET: Japanese NBI expert Team classification, SSL: sessile serrated lesion, LGD: low grade dysplasia, HGD: high grade dysplasia), [a]: Chi-square test, [b]: Fisher´s exact test. [c]: Wilcoxon-Mann-Whitney test.

Suppl. Table S10: Secondary outcomes and technical parameters (intention-to-treat dataset (if not specified otherwise))

	Cold snare-EMR 193 polyps	Hot snare-EMR 203 polyps	p
Technical success	178 (92.2%) [95%-CI: 87.5-95.3%]	198 (97.5%) [95%-CI: 94.4-98.9%]	**0.022**[a]
Resection speed (ITT analysis) (cm^2/h)	22.59 (±16.68; 1.88-117.81) [95%-CI: 20.19-24.98]	21.72 (±19.22; 1.18-144.51) [95%-CI: 19.04-24.40]	0.281[c]
Resection speed (PP analysis) (cm^2/h)	23.56 (±17.22; 1.88-117.81) [95%-CI: 20.94-26.18]	22.10 (±19.36; 1.18-144.51) [95%-CI: 19.36-24.84]	0.171[c]
Injection	141 (73.1%)	193 (95.1%)	**<0.001**[a]
Blue dye	114 (59.1%)	157 (77.3%)	
Adrenaline	45 (23.3%)	57 (28.1%)	
Use of >1 snare	41 (21.2%)	33 (16.3%)	0.203[a]
Reason for the change of snare			**<0.001**[b]
Technical failure	18/41 (43.9%)	1/33 (3.0%)	
Simplification of the resection	20/41 (48.8%)	30/33 (90.9%)	
Both	3/41 (7.3%)	2/33 (6.1%)	
Diameter of snares*			--
9mm	11 (5.7%)	2 (1.0%)	
10mm	112 (58.0%)	58 (28.6%)	
12mm	32 (16.6%)	0	
15mm	48 (24.9%)	139 (68.5%)	
20mm	1 (0.5%)	4 (2.0%)	
22mm	0	6 (3.0%)	
25mm	1 (0.5%)	5 (2.5%)	
30mm	2 (1.0%)	16 (7.9%)	
44mm	0	1 (0.5%)	
Number of pieces			**<0.001**[b]
En bloc	4 (2.1%)	17 (8.4%)	
2-5	56 (29.0%)	93 (45.8%)	
>5	133 (68.9%)	93 (45.8%)	
Additional resection	17 (8.8%)	21 (10.3%)	0.604[a]
Cold forceps	14 (7.3%)	7 (3.4%)	
Avulsion	3 (1.6%)	14 (6.9%)	
Additional prophylactic measures	41 (21.2%)	132 (65.0%)	**<0.001**[a]
Injection	1 (0.5%)	1 (0.5%)	1[b]
Hemoclips	36 (18.7%)	76 (37.4%)	**<0.001**[a]
Coagulation of adenoma	1 (0.5%)	11 (5.4%)	**0.005**[a]
Coagulation of vessels	1 (0.5%)	36 (17.7%)	**<0.001**[a]
Coagulation of margins	3 (1.6%)	62 (30.5%)	**<0.001**[a]
Hemostatic powder/gel	1 (0.5%)	1 (0.5%)	1[b]
Clipping of vessels **	23 (11.9%)	31 (15.3%)	0.331[a]
Clip-closure of the resection site**	26 (13.5%)	57 (28.1%)	**<0.001**[a]
Partial closure	2 (1.0%)	7 (3.4%)	
Complete closure	24 (12.4%)	50 (24.6%)	
Level of difficulty			0.441[a]
1 (easy)	79 (40.9%)	88 (43.3%)	
2 (normal)	74 (38.3%)	83 (40.9%)	
3 (difficult)	40 (20.7%)	32 (15.8%)	
Reasons for difficult resection			--
Inappropiate adjustability of the polyp	35/40 (87.5%)	26/32 (81.3%)	
Snare	8/40 (20.0%)	-	
Non-lifting	4/40 (10.0%)	10/32 (31.3%)	
Intraprocedural bleeding	6/40 (15.0%)	5/32 (15.6%)	
Sedation/patient-related	1/40 (2.5%)	4/32 (12.5%)	

ITT: Intention-to-treat analysis, PP: Per-protocol analysis, *Manufacturers of the used snares: Boston Scientific™/ Medwork™/ Meiners™/ Microtec™/ MTW™/ Olympus™/ Steris™/ US Endoscopy™/ Wieser™, IPB: Intra-procedural bleeding, **as treatment of IPB or prophylactic, [a]: Chi-square test, [b]: Fisher´s exact test, [c]: Wilcoxon-Mann-Whitney test.

Suppl. Table S11: Per-patient analysis of outcomes (intention-to-treat and per-protocol datasets)

	Cold snare-EMR	Hot snare-EMR	p	Odds ratio [95%-CI]
	ITT (n=184)	ITT (n=192)		
	Value [95%-CI]	Value [95%-CI]		
Major AE	2 (1.1%) [0.00 – 3.87 %]	15 (7.8%) [4.79 – 12.49 %]	**0.009**[a]	0.13 [0.03- 0.57
Perforation	0 [0- 2.00%]	7 (3.6%) [1.78-7.33 %]	**0.015**[b]	0.07 (0.00 – 1.18)
Post-procedural bleeding	2 (1.1%) [0.02-3.87 %]	9 (4.7%) [2.48 – 8.67 %]	**0.038**[a]	0.22 (0.05-1.05)
Intra-procedural bleeding	26 (14.1%) [9.93 – 20.10 %]	44 (22.9%) [17.53-29.36%]	**0.029**[a]	0.55 [0.32-0.94]
Postpolypectomy-syndrome	6 (3.3%) [1.50-6.93 %]	9 (4.7%) [2.58-8.67%]	0.480[a]	0.68 [0.24-1.96]
Residual/recurrent adenoma (first FU)	42/168 (25.0%) [19.06-32.05 %]	23/164 (14.0%) [9.53-20.16 %]	**0.013**[b]	2.04 [1.16 – 3.58]
Technical success	170 (92.4%) [87.63-95.41 %]	187 (97.4%) [94.04-98.89%]	**0.027**[a]	0.32 [0.11 – 0.92]
Resection speed (cm^2/h)	22.09 (±16.42; 1.88-117.81)	21.14 (±18.49; 2.98-144.51)	0.330[c]	-
	PP (n=165)	**PP (n=186)**	**P**	**Odds ratio [95%-CI]**
	Value [95%-CI]	**Value [95%-CI]**		
Major AE	2 (1.2%) [0.00-4.31 %]	14 (7.5%) [4.53-12.23 %]	**0.004**[a]	0.15 [0.03-0.67)
Perforation	0 [0 – 2.27%]	7 (3.8%) [1.83-7.56 %]	**0.016**[b]	0.07 [0.00-1.28]
Post-procedural bleeding	2 (1.2%) [0.00 - 4.31 %]	8 (4.3%) [02.19 – 8.25 %]	0.111[b]	0.27 (0.06-1.30)
Intra-procedural bleeding	18 (10.9%) [7.01-16.58 %]	42 (22.6%) [17.16-29.11 %]	**0.004**[a]	0.42 (0.23-0.76)
Postpolypectomy-syndrome	6 (3.6%) [1.68 -7.70 %]	9 (4.8%) [2.57 – 8.94 %]	0.578[a]	0.74 [0.26-2.13]
Residual/recurrent adenoma (first FU)	38/152 (25.0%) [18.79 – 32.44 %]	19/158 (12.0%) [7.83 – 18.01 %]	**0.003**[b]	2.44 [1.33 – 4.46]
Resection speed (cm^2/h)	23.02 (±16.94; 1.88-117.81)	21.52 (±18.63; 3.53-144.51)	0.206[c]	-

ITT: Intention-to-treat analysis, PP: Per-protocol analysis, AE: Adverse event, FU: Follow up, CI: Confidence interval, [a]: Chi-square test, [b]: Fisher´s exact test, [c]: Wilcoxon-Mann-Whitney U test.

Suppl. Table S12: Subgroups of major adverse events - characteristics and treatment (intention-to-treat dataset)

	All 396 polyps	Cold snare-EMR 193 polyps	Hot snare-EMR 203 polyps
Perforation	8	0	8
Time			
- intraprocedural	7 (87.5%)	-	7 (87.5%)
- <24 hours	1 (12.5%)	-	1 (12.5%)
- 24-48 hours	0	-	0
Sydney classification			
- Type 3	5 (62.5%)	-	5 (62.5%)
- Type 4	3 (37.5%)	-	3 (37.5%)
- Type 5	0	-	0
Maximum lesion diameter			
- 25mm	2	-	2
- 30mm	1	-	1
- 35mm	1	-	1
- 40mm	2	-	2
- 45mm	1	-	1
- 60mm	1	-	1
Localization			
- Cecum	2	-	2
- Ascending colon	4	-	4
- Transverse colon	1	-	1
Therapy			
- Observation	1 (12.5%)	-	1 (12.5%)
- Endoscopic therapy (hemoclips)	7 (87.5%)	-	7 (87.5%)
- Surgical therapy	0 (0%)	-	0 (0%)
Severity (AGREE [30])			
- I	0	-	0
- II	1	-	1
- IIIa	7	-	7
- IIIb	0	-	0
- IV	0	-	0
- V	0	-	0
Post-procedural bleeding	11	2	9
Time			
- <24 hours	8 (72.7%)	2 (100%)	6 (66.7%)
- 24-48 hours	1 (9.1%)	0	1 (11.1%)
- 2-7 days	2 (18.2%)	0	2 (22.2%)
Maximum lesion diameter			
- 25mm	3	0	3
- 30mm	3	1	2
- 40mm	2	0	2
- 45mm	1	0	1
- 60mm	2	1	1
Localization			
- Cecum	5	0	5
- Ascending colon	5	2	3
- Transverse colon	1	0	1
Therapy			
- Observation	2 (18.2%)	0	2 (22.2%)
- Endoscopic therapy	9 (81.8%)	2 (100%)	7 (77.8%)
- Surgical therapy	0	0	0
- Transfusion	1 (9.1%)	0	1 (12.5%)
Severity (AGREE [30])			
- I	1	0	1
- II	1	0	1
- IIIa	9	2	7
- IIIb	0	0	0
- IV	0	0	0
- V	0	0	0

EMR: Endoscopic mucosal resection, CSPEB: Clinically significant postendoscopic bleeding.

Suppl. Table S13: Intraprocedural bleeding and postpolypectomy-syndrome - characteristics and treatment (intention-to-treat dataset)

	All 396 polyps	Cold snare-EMR 193 polyps	Hot snare-EMR 203 polyps
Intra-procedural bleeding	73	27	46
Maximum lesion diameter			
- 20mm	8 (11.0%)	4 (14.8%)	4 (8.7%)
- 25mm	16 (21.9%)	5 (18.5%)	11 (23.9%)
- 30mm	22 (30.1%)	9 (33.3%)	13 (28.3%)
- 35mm	9 (12.3%)	4 (14.8%)	5 (10.9%)
- 40mm	5 (6.8%)	2 (7.4%)	3 (6.5%)
- 45mm	1 (1.4%)	0	1 (2.2%)
- 50mm	5 (6.8%)	1 (3.7%)	4 (8.7%)
- 55mm	1 (1.4%)	1 (3.7%)	0
- 60mm	4 (5.5%)	0	4 (8.7%)
- 70mm	1 (1.4%)	1 (3.7%)	0
- 80mm	1 (1.4%)	0	1 (2.2%)
Localization			
- Cecum	27 (37.0%)	15 (55.6%)	12 (26.1%)
- Ascending colon	23 (31.5%)	5 (18.5%)	18 (39.1%)
- Transverse colon	10 (13.7%)	3 (11.1%)	7 (15.2%)
- Descending colon	2 (2.7%)	1 (3.7%)	1 (2.2%)
- Sigmoid colon	6 (8.2%)	2 (7.4%)	4 (8.7%)
- Rectum	5 (6.8%)	1 (3.7%)	4 (8.7%)
Therapy			
- Injection	8 (11.0%)	5 (18.5%)	3 (6.5%)
- Hemoclips	36 (49.3%)	17 (6.0%)	19 (41.3%)
- Coagulation (snare)	38 (52.1%)	3 (11.1%)	35 (76.1%)
- Coagulation (forceps)	3 (4.1%)	1 (3.7%)	2 (4.3%)
- Argonplasmacoagulation	1 (1.4%)	1 (3.7%)	0
- Hemospray	2 (2.7%)	2 (7.4%)	0
Severity (AGREE [30])			
- No AE	73	27	46
Postpolypectomy-syndrome	15	6	9
Maximum lesion diameter			
- 20mm	5 (33.3%)	2 (33.3%)	3 (33.3%)
- 25mm	5 (33.3%)	3 (50.0%)	2 (22.2%)
- 30mm	2 (13.3%)	1 (16.7%)	1 (11.1%)
- 35mm	1 (6.7%)	0	1 (11.1%)
- 40mm	2 (13.3%)	0	2 (22.2%)
Localization			
- Cecum	5 (33.3%)	1 (16.7%)	4 (44.4%)
- Ascending colon	4 (26.7%)	2 (33.3%)	2 (22.2%)
- Transverse colon	3 (20.0%)	2 (33.3%)	1 (11.1%)
- Descending colon	1 (6.7%)	1 (16.7%)	0
- Sigmoid colon	1 (6.7%)	0	1 (11.1%)
- Rectum	1 (6.7%)	0	1 (11.1%)
Therapy			
- Observation only	8 (53.3%)	2 (33.3%)	6 (66.7%)
- Analgetics	2 (13.3%)	1 (16.7%)	1 (11.1%)
- Antibiotics	4 (26.7%)	3 (50.0%)	1 (11.1%)
- Analgetics+Antibiotics	1 (6.7%)	0	1 (11.1%)
Severity (AGREE [30])			
- No AE	1 (6.7%)	0	1 (11.1%)
- I	4 (26.7%)	2 (33.3%)	2 (22.2%)
- II	10 (66.7%)	4 (66.7%)	6 (66.7%)
- IIIa	0	0	0
- IIIb	0	0	0
- IV	0	0	0
- V	0	0	0

EMR: Endoscopic mucosal resection, CSPEB: Clinically significant postendoscopic bleeding.

Suppl. Table S14: Cases of residual/recurrent adenoma at 1st endoscopic follow up and in surgical specimen - characteristics and treatment (intention-to-treat dataset)

	Cold snare-EMR (193 polyps)	Hot snare-EMR (203 polyps)
Follow-up	177 (91.7%)	174 (85.7%)
Endoscopic	175	171
- with biopsy	141	142
Surgical specimen	2	3*
Residual neoplasia	42/177 (23.7%)	24/174 (13.8%)
Therapy		
Endoscopic	38 (90.5%)	22 (91.7%)
- Forceps	11 (26.2%)	8 (33.3%)
- polypectomy/EMR	11 (26.2%)	9 (37.5%)
- EMR+coagulation	13 (31.0%)	1 (4.2%)
- Forceps+ coagulation	0	2 (8.3%)
- EFTR	2 (4.8%)	2 (8.3%)
- EFTR+EMR	1 (2.4%)	0
Surgical	4 (9.5%)	2 (8.3%)
Histology		
- Sessile serrated lesion	7 (16.7%)	3 (12.5%)
- Tubular adenoma LGD	17 (40.5%)	13 (54.2%)
- Tubular adenoma HGD	1 (2.4%)	3 (12.5%)
- Tubulovillous adenoma LGD	7 (16.7%)	3 (12.5%)
- Tubulovillous adenoma HGD	2 (4.8%)	1 (4.2%)
- Villous adenoma LGD	1 (2.4%)	0
- Villous adenoma HGD	2 (4.8%)	0
- Mixed polyp	1 (2.4%)	0
- Adenocarcinoma	4 (9.5%)**	1 (4.2%)***
R0	9 (21.4%)	3 (12.5%)

EMR: Endoscopic mucosal resection, EFTR: Endoscopic full thickness resection, LGD: low grade dysplasia, HGD: high grade dysplasia, *: in 1 case no residual tumor, **: 2 cases from surgical specimen and 2 cases from endoscopic FU after 5 and 12 months, ***: from surgical specimen.

Suppl. Table S15: Uni- and multivariable regression analysis of possible predictive factors for major AE in the intention-to-treat dataset

Variable	Univariable analysis		Multivariable analysis	
Impact on major AE - ITT				
	n	**p**	**Odds ratio [95%-CI]**	**p**
Age	18	0.595	--	--
Sex				
- male*	11		--	--
- female	7	0.471		
ASA				
- I*	4		--	--
- II	12	0.212		
- III	2	0.216		
Antiplatelet-/Anticoagulant therapy				
- No*	13		--	--
- Yes	5	0.781		
Operator	**	0.723****		
Participating centers				
- Low volume (=1 patient per month) *	4		--	--
- Medium volume (=2 patients per month)	9	0.278		
- High volume (≥3 patients per month)	5	0.707		
Localization				
- Right colon*	0		--	--
- Left colon	18	0.769		
- Rectum	0	0.885		
Maximum polyp diameter				
- <4cm*	8			
- ≥4cm	10	**0.011**	**3.37** [1.25-9.09]	**0.016**
Submucosal injection				
- No*	2		--	--
- Yes	16	0.589		
Number of pieces				
- 1-5*	5		--	--
- >5	13	0.192		
Intraprocedural bleeding				
- No*	12			
- Yes	6	**0.104**	1. 72 (0.58 - 5.07)	0.329
Additional prophylactic procedures				
- No*	9		--	--
- Yes	9	0.581		
Clipping of vessels* **				
- No*	15		--	--
- Yes	3	0.702		
Clip-closure of the resection site* **				
- No*	15		--	--
- Complete	3	0.786		
- Partial	0	0.847		
Prophylactic coagulation of vessels				
- No*	14			
- Yes	4	**0.066**	1.31 [0.29-6.01]	0.724
Prophylactic coagulation of residual adenoma				
- No*	17		--	--
- Yes	1	0.530		
Prophylactic coagulation of margins				
- No*	12			
- Yes	6	**0.056**	2.15 [0.56-8.26]	0.263
Level of difficulty				
- Easy*	6		--	--
- Middle	7	0.692		
- Difficult	5	0.265		
Histology				
- SSL/hyperplastic polyp*	8		--	--
- Adenoma LGD	6	0.302		
- Adenoma HGD/Carcinoma	4	0.908		

ITT: Intention-to-treat analysis, *: Reference, **: not shown, ***as treatment of intra-procedural bleeding or prophylactically, **** overall model fit (p > 0.05 indicates that the full model (operator) does not provide a significantly better fit to the data than the null model), SSL: sessile serrated lesion, LGD: low grade dysplasia, HGIEN: high grade dysplasia, CI: confidence interval.

Suppl. Table S16: Uni- and multivariable regression analysis of possible predictive factors for residual adenoma/neoplasia at the first FU examination in the intention-to-treat dataset

Variable	Univariable analysis		Multivariable analysis	
Impact on residual adenoma/neoplasia - ITT				
	n	**p**	**Odds ratio [95%-CI]**	**p**
Age	66	0.209	--	--
Sex				
- male*	34		--	--
- female	32	0.885		
ASA				
- I*	21		--	--
- II	39	0.372		
- III	6	0.201		
Antiplatelet-/Anticoagulant therapy				
- No*	53		--	--
- Yes	13	0.436		
Operator	**	0.353****	-	-
Participating centers				
- Low volume (=1 patient per month) *	23		--	--
- Medium volume (=2 patients per month)	22	0.864		
- High volume (≥3 patients per month)	21	0.613		
Localization				
- Right colon*	56			
- Left colon	6	0.932	0.77 [0.28-2.16]	0.627
- Rectum	4	**0.098**	2.09 [0.46-9.46]	0.236
Maximum polyp diameter				
- <4cm*	37			
- ≥4cm	29	**<0.001**	**2.47** [1.21-5.03]	**0.013**
Submucosal injection				
- No*	8			
- Yes	58	0.416		
Number of pieces				
- 1-5*	52			
- >5	14	**<0.001**	1.74 [0.84-3.61]	0.135
Intraprocedural bleeding				
- No*	52		--	--
- Yes	14	0.532		
Additional prophylactic procedures				
- No*	40		--	--
- Yes	26	0.477		
Clipping of vessels* **				
- No*	52		--	--
- Yes	14	0.108		
Clip-closure of the resection site* **				
- No*	57		--	--
- Complete	9	0.340		
- Partial	0	0.750		
Prophylactic coagulation of vessels				
- No*	62		--	--
- Yes	4	0.275		
Prophylactic coagulation of residual adenoma				
- No*	62			
- Yes	4	**0.096**	2.37 [0.53-10.60]	0.259
Prophylactic coagulation of margins				
- No*	59		--	--
- Yes	7	0.126		
Level of difficulty				
- Easy*	18			
- Middle	26	0.147	1.11 [0.55-2.23]	0.774
- Difficult	22	**<0.001**	1.73 [0.75-3.98]	0.198
Histology				
- SSL/hyperplastic polyp*	12			
- Adenoma LGD	28	**0.047**	1.75 [0.83-3.70]	0.143
- Adenoma HGD/Carcinoma	26	**<0.001**	**2.92** [1.22-7.00]	**0.016**

ITT: Intention-to-treat analysis, *: Reference, **: not shown, ***as treatment of intra-procedural bleeding or prophylactically, **** overall model fit (p > 0.05 indicates that the full model (operator) does not provide a significantly better fit to the data than the null model), SSL: sessile serrated lesion, LGD: low grade dysplasia, HGD: high grade dysplasia, CI: confidence interval.

WHAT YOU NEED TO KNOW

Background and context: Hot snare-EMR is the standard therapy for the resection of non-pedunculated polyps ≥2cm but major AE are a clinically relevant problem.
New Findings: In this randomized-controlled trial, cold snare-EMR appeared safer than hot snare resection with an almost complete elimination of major AE but resulted in a higher rate of residual neoplasia. However, in selected lesions this drawback only appears to be 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.
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 (e.g. additional margin coagulation) to make it more effective.

LAY SUMMARY

Cold resection of large non-pedunculated colorectal polyps appears safer than the hot technique with an almost complete elimination of major AE, however at the cost of a higher rate of residual neoplasia.