Accepted Manuscript

Submission Date: 2023-04-25
Accepted Date: 2024-03-22
Accepted Manuscript online: 2024-04-15

Endoscopy International Open

Safety of Cold Resection of Non-ampullary Duodenal Polyps: A Systematic Review and Meta-analysis

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DOI: 10.1055/a-2306-6535

Please cite this article as: Tayar E, Ladna M, King W et al. Safety of Cold Resection of Non-ampullary Duodenal Polyps: A Systematic Review and Meta-analysis. Endoscopy International Open 2024. doi: 10.1055/a-2306-6535

Conflict of Interest: Dr. Qumseya is a consultant for Medtronic, Assertio Management, and Endogastric Solutions, and is a speaker for Castle Biosciences.
All of the other authors confirm that they have no conflicts of interest

Abstract:
Introduction: Endoscopic resection has traditionally involved electrosurgical cautery (hot snare) to resect premalignant polyps. Recent data have suggested superior safety of cold resection. We aimed to assess the safety of cold compared to traditional (hot) resection for non-ampullary duodenal polyps.
Methods: We performed a systematic review ending in September 2022. The primary outcome of interest was the adverse event (AE) rate for cold compared to hot polyp resection. We reported odds ratios with 95% confidence intervals (CIs). Secondary outcomes included rates of polyp recurrence and post-polypectomy syndrome. We assessed publication bias with the classic fail-safe test and used forest plots to report pooled effect estimates. We assessed heterogeneity using I2 index.
Results: Our systematic review identified 1,215 unique citations. 8 of these met inclusion criteria, 7 of which were published manuscripts and 1 of which was a recent meeting abstract. On random effect modeling, cold-resection was associated with significantly lower odds of delayed bleeding compared to hot-resection. The difference in the odds of perforation (OR 0.31 [95% CI:0.05 – 2.87], p=0.2, I2=0) and polyp recurrence (OR 0.75 [95% CI:0.15 – 3.73], p=0.72, I2=0) between hot and cold resection was not statistically significant. There were no cases of post-polypectomy syndrome reported with either hot or cold techniques.
Conclusion: Cold resection is associated with lower odds of delayed bleeding compared to hot resection for duodenal tumors. There was a trend toward higher odds of perforation and recurrence following hot resection, but this trend was not statistically significant.

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Study	Study type	Pub type	Procedure	Sample size (# lesions)	Sample size (# patients)	% Male	Mean age (yrs)	Poly size included (mm)	Mean polyp size (mm)	Delayed bleed	Perforation	# of endoscopists	Qumseya score
Beany 2022	Retrospective, comparative	Abstract	EMR	57	57	51.4	65.25	>10	25.5	0 cold 6 hot	0 cold 1 hot	NR	NR
Trivedi 2022	Retrospective, comparative	paper	HSP (66.2% EMR) CSP (37% EMR)	120	41 cold 69 hot	68 cold 49 hot	72 cold 68 hot	≥5	12 cold 15 hot	0 cold 6 hot	0 cold 1 hot	7	8
Repici 2022	Retrospective, comparative	paper	EMR	NR	33 cold 101 hot	55 cold 42 hot	63 cold 68 hot	NR	NR	0 cold 1 hot	0 cold 10 hot	4 European Centers	6
Takizawa 2021	Prospective, non-comparative	paper	CSP	21	21	76.2	71	≤10	8	0	0	4	7
Daisuke 2017	Prospective, non-comparative	paper	CSP + CFP	39	30	66.7	64.1	<6	3.9	0	0	1	6
Okimoto 2021	Retrospective, non-comparative	paper	CSP	46	35	68.6	66.6	<10	4.2	0	0	NR	6
Dang 2022	Retrospective, non-comparative	paper	CSP	39	39	30.8	66.8	>10	26.6	1	0	5	6
Okimoto 2021	Retrospective, non-comparative	paper	CSP + CFP	57	44	68.1	66	<10	3	0	0	NR	6

Table: Patient and study characteristics of each of the included studies. C-EMR = cold endoscopic mucosal resection. H-EMR = hot endoscopic mucosal resection. CSP = cold snare polypectomy. HSP = hot snare polypectomy. NR = not reported

Topic: Safety of Cold Resection of Non-ampullary Duodenal Polyps: A Systematic Review and Meta-analysis

Principal Investigator: Dr. Bashar Qumseya

P: Patients with Polyps (Colon, Gastric, Duodenal)
I: Cold-Snare Polypectomy
C: Hot-Snare Polypectomy
O: Adverse events

Database: Ovid MEDLINE ALL
Search Date: December 9, 2021
Search Results: 293
UPDATE: December 9, 2021 - September 23, 2022 Update Search Results: 107
UPDATE: September 24, 2022 – April 29, 2023 Update Search Results: 65

1. Polyps/ or exp Intestinal Polyps/ or Adenomatous Polyps/ or exp Intestinal Polyposis/
2. ((colorect* or colon* or large bowel or large intestin* or small intestin* or small bowel or rect* or anal or anus or anuses or gastric or gastro* or stomach* or duoden* or gastroduodenal or pyloroduodenal or sessile or serrated or pedunculated) and (polyp* or adenoma* or lesion*)).tw,kf.
3. 1 or 2
4. ((cold-snar* or "cold snar*" or hot-snar* or "hot snar*") and (resect* or polypectom*)).tw,kf.
5. (((snare or snares or snaring or snared or minisnare or wire) adj3 (resect* or polypectom*)) and (hot or cold)).tw,kf.
6. 4 or 5
7. 3 and 6
8. limit 7 to rd=20220924-20231231

Database: Embase.com (Elsevier)
Search Date: December 9, 2021
Search Results: 869
UPDATE: December 9, 2021 - September 23, 2022 Update Search Results: 202
UPDATE: September 24, 2022 – April 29, 2023 Update Search Results: 78

1.'polyp'/de OR 'adenomatous polyp'/de OR 'polyposis'/exp OR 'intestine polyp'/exp OR 'rectum polyp'/exp OR 'stomach gland polyp'/de or 'stomach polyp'/exp
2.((colorect* OR colon* OR large bowel OR large intestin* OR small intestin* OR small bowel OR rect* OR anal OR anus OR anuses OR gastric OR gastro* OR stomach* OR duoden* OR gastroduodenal OR pyloroduodenal OR sessile OR serrated OR pedunculated) AND (polyp* OR adenoma* OR lesion*)):ti,ab,kw
3.#1 OR #2
4.(cold-snar* OR "cold snar*" OR hot-snar* OR "hot snar*"):ti,ab,kw AND ((resect* OR polypectom*):ti,ab,kw OR 'polypectomy'/exp)

5.((snare OR snares OR snaring OR snared OR minisnare OR wire) NEAR/3 (resect* OR polypectom*)):ti,ab,kw
6.(hot OR cold):ti,ab,kw AND 'polypectomy'/exp
7.#5 AND #6
8.#4 OR #7
9.#3 AND #8
10. #9 AND [24/09/2022]/sd

Database: Cochrane Library (Wiley)
Search Date: December 9, 2021
Search Results: 186
September 19, 2022 Update Search Results: 214
UPDATE: December 9, 2021 - September 23, 2022 Update Search Results: 33
UPDATE: September 24, 2022 – April 29, 2023 Update Search Results: 17

1. [mh Polyps] OR [mh "Intestinal Polyps"] OR [mh "Adenomatous Polyps"] OR [mh "Intestinal Polyposis"]
2. ((colorect* OR colon* OR large bowel OR large intestin* OR small intestin* OR small bowel OR rect* OR anal OR anus OR anuses OR gastric OR gastro* OR stomach* OR duoden* OR gastroduodenal OR pyloroduodenal OR sessile OR serrated OR pedunculated) AND (polyp* OR adenoma* OR lesion*)):ti,ab,kw
3. #1 OR #2
4. ((cold-snar* OR "cold snar*" OR hot-snar* OR "hot snar*") AND (resect* OR polypectom*)):ti,ab,kw
5. (((snare OR snares OR snaring OR snared OR minisnare OR wire) NEAR/3 (resect* OR polypectom*)) AND (hot or cold)):ti,ab,kw
6. #4 OR #5
7. #3 AND #6

Database: Web of Science (Science Citation Index Expanded [SCI-EXPANDED] – 1900-present; Conference Proceedings Citation Index – Science [CPCI-S]—1993-present)
Search Date: December 9, 2021
Search Results: 255
UPDATE: December 9, 2021 - September 23, 2022 Update Search Results: 37
UPDATE: September 24, 2022 – April 29, 2023 Update Search Results: 26

1. TI=((colorect* OR colon* OR large bowel OR large intestin* OR small intestin* OR small bowel OR rect* OR anal OR anus OR anuses OR gastric OR gastro* OR stomach* OR duoden* OR gastroduodenal OR pyloroduodenal OR sessile OR serrated OR pedunculated) AND (polyp* OR adenoma* OR lesion*)) OR AB=((colorect* OR colon* OR large bowel OR large intestin* OR small intestin* OR small bowel OR rect* OR anal OR anus OR anuses OR gastric OR gastro* OR

stomach* OR duoden* OR gastroduodenal OR pyloroduodenal OR sessile OR serrated OR pedunculated) AND (polyp* OR adenoma* OR lesion*))
2. TI=((cold-snar* OR "cold snar*" OR hot-snar* OR "hot snar*") AND (resect* OR polypectom*)) OR AB=((cold-snar* OR "cold snar*" OR hot-snar* OR "hot snar*") AND (resect* OR polypectom*))
3. TI=(((snare OR snares OR snaring OR snared OR minisnare OR wire) NEAR/3 (resect* OR polypectom*)) AND (hot OR cold)) OR AB=(((snare OR snares OR snaring OR snared OR minisnare OR wire) NEAR/3 (resect* OR polypectom*)) AND (hot OR cold))
4. #2 OR #3
5. #1 AND #4

Database: CINAHL Plus with Full Text
Search Date: December 9, 2021
Search Results: 124
September 19, 2022 Update Search Results: 142
UPDATE: December 9, 2021 - September 23, 2022 Update Search Results: 27
UPDATE: September 24, 2022 – April 29, 2023 Update Search Results: 13

1. (MH "Polyps") OR (MH "Intestinal Polyps+") OR (MH "Adenomatous Polyps+") OR (MH "Intestinal Polyposis+")
2. TI((colorect* OR colon* OR large bowel OR large intestin* OR small intestin* OR small bowel OR rect* OR anal OR anus OR anuses OR gastric OR gastro* OR stomach* OR duoden* OR gastroduodenal OR pyloroduodenal OR sessile OR serrated OR pedunculated) and (polyp* OR adenoma* OR lesion*)) OR AB((colorect* OR colon* OR large bowel OR large intestin* OR small intestin* OR small bowel OR rect* OR anal OR anus OR anuses OR gastric OR gastro* OR stomach* OR duoden* OR gastroduodenal OR pyloroduodenal OR sessile OR serrated OR pedunculated) and (polyp* OR adenoma* OR lesion*))
3. S1 OR S2
4. TI((cold-snar* OR "cold snar*" OR hot-snar* OR "hot snar*") AND (resect* OR polypectom*)) OR AB((cold-snar* OR "cold snar*" OR hot-snar* OR "hot snar*") AND (resect* OR polypectom*))
5. TI(((snare OR snares OR snaring OR snared OR minisnare OR wire) N3 (resect* OR polypectom*)) AND (hot OR cold)) OR AB(((snare OR snares OR snaring OR snared OR minisnare OR wire) N3 (resect* OR polypectom*)) AND (hot OR cold))
6. S4 OR S5
7. S3 AND S6

Introduction:

Tumors of the duodenum are rare compared to those of other parts of the GI tract. [1] Duodenal carcinomas represent a mere 0.5% of all malignant gastrointestinal tumors. Among patients undergoing esophagogastroduodenoscopy (EGD), the prevalence of duodenal polyps is 0.4%. [2,3] When polyps are detected, though, the duodenum presents a particularly challenging location for resection. [1,4,5] Both surgical and endoscopic resection of duodenal polyps can be complex and invasive due to anatomical restrictions such as the anatomical proximity to the head of the pancreas and the biliary system.[2,6] Endoscopic submucosal dissection (ESD) within the duodenum has been shown to be especially difficult and prone to adverse events such as bleeding and perforation due to the very thin muscular layer of the duodenum. [7,8-10]

Resection of duodenal polyps can be done by cold or hot resection. Cold resection includes cold snare polypectomy (CSP, without submucosal injection), or by cold endoscopic mucosal resection (c-EMR). Hot or traditional resection includes hot snare polypectomy (HSP) or hot-EMR. EMR is a well-established technique that has been shown to be safe and effective method for rection of duodenal polyps. [11] Traditional EMR carries a small risk of bleeding and perforation. [12] Cold resection methods have recently been gaining momentum as safer alternatives to hot resection for treatment of colonic polyps, and limited data have supported its use in the duodenum as well. [7,13-15] The absence of thermal injury to the muscularis propria is thought to reduce rates of delayed bleeding and perforation. However, robust data on use of cold resection in the duodenum remain sparse.

We therefore aimed to conduct a systematic review and meta-analysis comparing cold resection versus hot resection of non-ampullary duodenal polyps and to compare rates of early and delayed adverse events between the two techniques.

Methods

Study Selection

This study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using a protocol developed a priori by the study team. [16] Our protocol was not registered. We included all studies of nonampullary duodenal polyps that included CSP or C-EMR or compared these techniques to HSP or H-EMR. Inclusion criteria were as follows: (I) randomized controlled clinical trials, prospective studies, retrospective studies, or meeting abstracts from 2017-2022; (II) studies that were published in peer-reviewed journals; (III) endoscopically diagnosed nonampullary duodenal polyps (biopsy before treatment was not necessary). Studies were excluded if they were: (I) studies of ampullary polyps or lesions; (II) case reports or case series (10 or less patients); (III) English language full text were not available.

Search strategy and data extraction

The literature search was conducted with the help of an expert health science librarian (RR). We searched MEDLINE (Ovid), Web of Science, Embase, Cochrane Library and CENTRAL, and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) from inception. Details of our search strategy are listed in Appendix 1. The last update of the search was in September 2022. The PRISMA 2020 checklist can be found in Appendix 2. Citations

were saved as an EndNote library (Thompson Reuters, Carlsbad, California, United States) then imported into Covidence (Covidence.org). Duplicates were removed in both EndNote and Covidence. We reviewed the studies via titles and abstracts. Studies were excluded if they were not original articles (i.e., reviews, case reports, case series, editorials, or conference papers), or were irrelevant to the study topic. Based on our review of the full text, 8 papers were included in the final meta-analysis.

For each study the following data was extracted: primary author, publication journal and year, country/countries where the study was carried out, study design, number of patients, distribution of patient age, patient gender, race (if reported), endoscopic equipment, endoscopic techniques, number of endoscopists in the study, prevalence of duodenal polyps in the study population (if reported), mean and range of polyps' sizes, morphology and histology of polyps, en-bloc resection rate, rates of complete resection with each technique , and post-procedure adverse events (early bleeding, delayed bleeding, transfusion need, early perforation, delayed perforation, readmission, polypectomy syndrome, and polyp recurrence rate following complete resection).

Outcome of Interest and Quality Assessment

The study was designed based on the PICO (population, intervention, control, and outcomes) format. The population of interest were patients with duodenal polyps who had polypectomy. The intervention was cold resection; the comparator was hot resection. Outcomes of interest included: adverse events, residual polyp rate, recurrent polyp rate, and cost-effectiveness.

Adverse events included: early bleeding (defined as bleeding that occurred during the procedure or within 24-hours), delayed bleeding (defined as bleeding that occurred more than 24 hours after the procedure), early perforation (documented by cross-sectional imaging or endoscopy), delayed perforation (perforation more than 24 hours after the procedure), blood transfusion need, re-admission (defined as patient being readmitted for a polypectomy complication), post-polypectomy syndrome, residual polyp rate (defined as histology-confirmed residual polyp on biopsies done during procedure), and recurrent polyp rate (defined as finding polyp tissue at the site of previous polypectomy on follow up endoscopy). EMR was defined as submucosal injection with a lifting solution followed by resection using a snare. Many patients with bleeding required endoscopic intervention (cautery, injection with epinephrine, or clipping). In a sensitivity analysis, we identified the rate of delayed bleeding in H-EMR. We used the historic data to perform an indirect analysis comparing the rates of bleeding in CSP (as identified by our study) compared to HSP (as identified from previous meta-analysis).

We used the Quality Assessment for Meta-Analysis Scoring system (Qumseya scale) for quality assessment of individual studies. [17] Quality assessment was conducted only for the manuscripts that were included, since abstracts lack sufficient information to properly assess their quality. The results were reported quantitatively. Studies deemed to be outliers or of low quality were removed from the analysis. Studies were deemed to be outliers based on an effect estimate that was 6-8 times higher or lower than the pooled effect estimate, as previously reported. [18,19]

Statistical analysis

The primary effect estimate was the odds ratio (OR) of adverse events in cold compared to hot techniques (for comparative studies). All analyses were done per patient (not per polyp). We decided a priori to use random effect modeling, DerSimonian and Laird, in all analyses. We reported outcomes using forest plots. We used I^2 (the ratio of true heterogeneity to total observed variation) to measure heterogeneity. We used the classic fail-safe test to check for publication bias. For studies with no patients having the outcome of interest, a correction number of 0.1 was used instead of zero. We used CMA V3 (BioSTAT, Inc., Englewood, New Jersey, USA) for all statistical analyses.

Results

Our searches resulted in 3,748 citations. Of these, 2,533 were removed as duplicates; 1,215 were screened by title and abstract; 722 were excluded as irrelevant by title and abstract, leaving for 493 for detailed review. Of these, 8 met inclusion criteria [7,20-26] and were included in the analysis. Seven [7,21-26] were published manuscripts, and one [20] was a recent meeting abstract **(Figure 1)**. These 8 studies included 470 patients. Mean polyp size ranged from 3 to 25.5 mm. An example of cold snare resection from the authors' institution is shown in **Figure 2.**

We identified 3 comparative studies [20-22], (1 prospective and 2 retrospective). Two of these studies [20,22] compared hot and cold EMR. The third study [21] included a mix of EMR and CSP (Table 1). A total of 206 patients underwent polypectomy with hot resection, of whom 39 suffered delayed bleeding. There were no cases of delayed bleeding reported in the 95 patients who underwent cold resection. On random effect modeling, the odds of delayed bleeding was

significantly lower in cold resection compared hot resection (OR 0.067 95% CI:[0.013-0.35], p=0.001. No heterogenicity was detected with I^2=0%, **(Figure 3a).**

From the five non-comparative studies [7,23-26] there was one confirmed case of delayed bleeding [25] out of 169 patients who had polypectomy with cold resection. On meta-analysis, using random effect modeling, the pooled odds of delayed bleeding for resection was 2% (95% CI:[1.3-3.2%], p<0.001, **(Figure 3b).** No heterogenicity was detected, with I^2=0%. Removing the data from the only abstract did not change the results (1.6% (95% CI:[0.3-8.6%]), p<0.001, I^2=0).

The comparative studies reported no cases of perforation with cold resection (0 out of 95), whereas there were 12 cases of perforation (early or delayed) out of 206 treated with hot techniques. This difference did not reach statistical significance on meta-analysis (OR 0.31 (95% CI:[0.05-2.87]), p=0.2, I^2=0). Similarly, there were no early or delayed perforations reported in the non-comparative studies.

Polyp recurrence was noted in 9 of 95 patients who had cold resection, compared to 30 of 206 patients treated with hot techniques. On meta-analysis, there was a trend toward a lower recurrence rate in the cold resection group compared to the hot resection, but this trend was not statistically significant (OR 0.75 (95% CI:[0.15-3.73]), p=0.72, I^2=0), (**Figure 4a)**. The non-comparative studies that reported polyp recurrence had follow-up times ranging from 6 months to 3 years. All studies defined recurrence as histologically confirmed dysplastic or metaplastic tissue at follow-up surveillance colonoscopy. One study [24] was removed from the pooled

analysis due to being an outlier. The pooled rate of polyp recurrence was 2.9% (95% CI:[1%-8.5%], p<0.001, I^2=0%), (**Figure 4b**).

Quality assessment and Publication bias

All included studies had adequate scores on the Qumseya scale. [16] Funnel plots were not assessed due to the low number of studies (10 studies are generally required to generate an adequate funnel plot). However, using the fail-safe test, we found that the risk of publication bias was low; 26 negative studies would be needed to bring the p-value to > 0.05).

Discussion

In this systematic review and meta-analysis, we report that cold resection (CSP and C-EMR) of non-ampullary duodenal polyps is associated with lower adverse event rates than hot resection (HSP and H-EMR). Cold resection was associated with lower rates of early bleeding, delayed bleeding, and perforation. Rates of polyp recurrence were similar in both groups. To our knowledge, this is the first systematic review with meta-analysis to evaluate cold resection compared to hot resection for duodenal polyps.

Clinical Implications

Despite the low rate of adenomas and carcinomas in the duodenum compared to the colon, duodenal polyps requiring endoscopic resection are often encountered, especially in tertiary centers and advanced endoscopy programs. [27] The elevated rate of adverse events in the

duodenum is multifactorial; the thinner duodenal wall, increased vascular supply around the head of pancreas, and impaired endoscopic maneuverability within the duodenum likely all play contributing roles. [28] Rates of delayed bleeding in our pooled analysis of hot resection (39 out of 206) are consistent with bleeding rates of 18 to 22% quoted in prior studies. [5,6,29,30] In comparison, delayed bleeding following cold resection occurred in only one of the 169 patients in the observational studies and none of the patients in the comparative ones.

Perforation is the most serious and second most common potential complication of polypectomy. [31] A recent literature review from Switzerland showed that 2 out of 78 patients diagnosed with non-ampullary duodenal adenomas suffered from early perforation during traditional hot-snare polypectomy (2.6%). [32] Fortunately, both of these perforations were treated with an over-the-scope clip device. [33] On the other hand, our systematic review found that cold techniques carry a lower rate of perforation. Given the rarity of perforation, the statistical significance of this finding suggests a substantial difference in perforation risk between the two modalities. We suggest that by sparing patients electrocautery, cold resection protects the thin muscularis layer, thereby minimizing perforation risk. Although the anatomy and technical details of polypectomy in the colon are vastly different, it is notable that emerging data from the lower GI tract have supported a similar conclusion. [33]

A common justification for electrocautery is its higher chances of achieving en bloc resection. We did not report this outcome because it is self-evident that cold resection is much less likely to achieve en bloc resection of large (>10 mm) polyps. However, this is the same reason that cold resection has a superior safety profile; it cannot cut through deeper submucosal blood vessels or

injure the muscularis propria. In addition, we argue that en bloc resection is unnecessary for most duodenal polyps. In our experience, most polyps encountered in general endoscopy and even in advanced endoscopy practices can safely be removed piecemeal. This point is further supported by the similar rates of recurrence across hot and cold resections as well as the low overall recurrence rate of 2.9% in cold resection studies. As noted in the results, we excluded one study [25] from this analysis since the study reported 18 recurrences among 39 patients, a rate much higher than expected and that may represent a poor technique or early learning experience.

Our systematic review did not identify a study analyzing cost-effectiveness of cold resection. One of the manuscripts [25] did speculate on how procedure time, complication rates, and timing of surveillance endoscopy may impact cost. One prospective non-comparative study [34], which was excluded from the meta-analysis, mentioned an increase in health care costs following "not negligible number of bleeding episodes following HSP."

Therefore, we believe that the benefits of en bloc resection with hot techniques are outweighed by the increased rate of adverse events. The authors postulate that an evidence-based shift to cold resection would result in a significant drop in adverse event rates.

Strengths and Limitations

There are several strengths to our systematic review and meta-analysis. To our knowledge, this is the first meta-analysis to compare cold versus hot techniques for resection of duodenal polyps with adverse events as the primary outcome of interest. Secondly, our study focused on

comparative studies but used observational studies as supportive evidence. The heterogeneity was low in all comparisons.

Our analysis does have several limitations. Firstly, the number of studies included was low, with most of them being non-comparative and none of them being randomized control trials. Therefore, the overall quality of the included data is likely low to moderate. Secondly, many of the cohort studies were small, retrospective, and single center. In addition, we cannot rule out some patient overlap in some of the studies. For example, three of the included studies [23,24,26] were from the same center but were conducted at different time periods. Furthermore, there was widespread variation in definitions of adverse events. For example, the amount of blood loss required to count as "early bleeding" ranged from any visible oozing at the site to brisk bleeding requiring blood transfusion. Additionally, the rates of adverse events are low overall, thus lowering the power of the study to detect some differences. Finally, the follow up times for assessment of recurrence ranged from six months to three years.

Conclusions

This systematic review and meta-analysis showed that cold resection for non-ampullary duodenal polyps caused fewer adverse events than the traditional hot techniques without any significant difference in adenoma recurrence rates. This meta-analysis supports the routine use of cold polypectomy techniques as first line over hot polypectomy techniques for such duodenal polyps. These findings are consistent with recent data from other parts of the GI tract that cold resection is safer than hot resection. Our results add to the mounting evidence that cold resection

techniques should be more widely adopted in order to minimize risks of delayed bleeding and perforation in duodenal polyps.

Figure 1: PRISMA plot of the included studies

Table 1: Patient and study characteristics of each of the included studies. C-EMR = cold endoscopic mucosal resection. H-EMR = hot endoscopic mucosal resection. CSP = cold snare polypectomy. HSP = hot snare polypectomy. NR = not reported

Figure 2: a) 15 mm duodenal adenoma and b) same location after cold snare resection

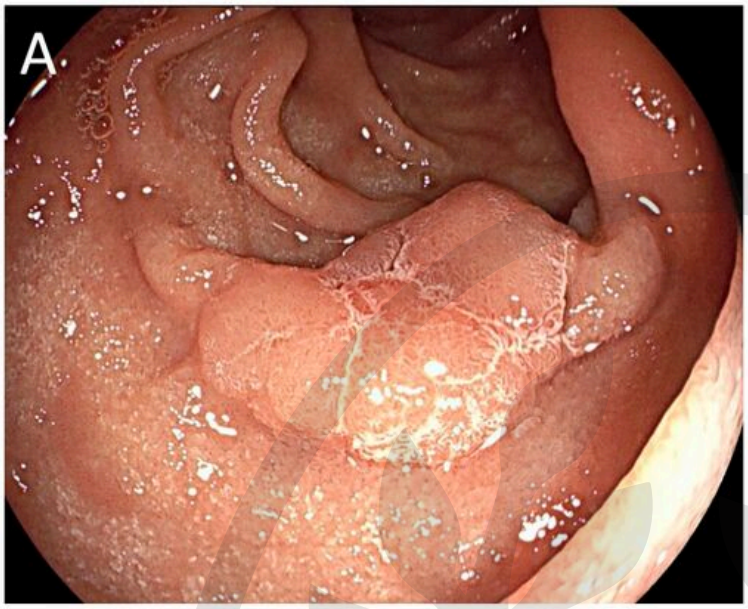
Figure 3: Forest plots of the a) odds of delayed bleeding in cold compared to hot resection of duodenal lesions; b) rates of delayed bleeding in cold resection of duodenal polyps; and c) odds of perforation in cold compared to hot EMR of duodenal lesions.

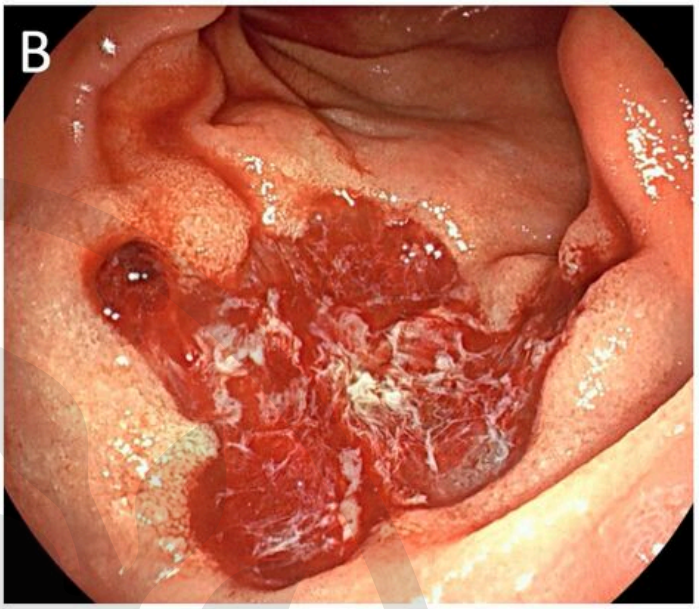
Figure 4: Forest plots of: a) odds of polyp recurrence in cold compared to hot resection of duodenal polyps; and b) rates of polyp recurrence after cold resection of duodenal lesions.

References

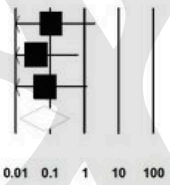
1. Endo M, Abiko Y, Oana S, et al. USEFULNESS OF ENDOSCOPIC TREATMENT FOR DUODENAL ADENOMA. *Digestive Endoscopy*. 2010;22(4):360-365. doi:10.1111/J.1443-1661.2010.01014.
2. Alwmark A, Andersson A, Lasson A. Primary carcinoma of the duodenum. *Annals of Surgery*. 1980;191(1):13. doi:10.1097/00000658-198001000-00003
3. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The Epidemiology and Pathogenesis of Neoplasia in the Small Intestine. *Annals of epidemiology*. 2009;19(1):58. doi:10.1016/J.ANNEPIDEM.2008.10.004
4. Honda T, Yamamoto H, Osawa H, et al. Endoscopic submucosal dissection for superficial duodenal neoplasms. *Dig Endosc*. 2009;21(4):270-274. doi:10.1111/j.1443-1661.2009.00908.x
5. Oka S, Tanaka S, Nagata S, et al. Clinicopathologic features and endoscopic resection of early primary nonampullary duodenal carcinoma. *J Clin Gastroenterol*. 2003;37(5):381-386. doi:10.1097/00004836-200311000-00006
6. Tsuji S, Doyama H, Tsuji K, et al. Preoperative endoscopic diagnosis of superficial non-ampullary duodenal epithelial tumors, including magnifying endoscopy. *World J Gastroenterol*. 2015;21(41):11832. doi:10.3748/WJG.V21.I41.11832
7. Takizawa K, Kakushima N, Tanaka M, et al. Cold snare polypectomy for superficial non-ampullary duodenal epithelial tumor: a prospective clinical trial (pilot study). *Surg endosc*. 2022;36(7):5217-5223. doi:10.1007/S00464-021-08899-9
8. Matsuda Y, Sakamoto K, Kataoka N, Yamaguchi T, Tomita M, Makimoto S. Perforation associated with endoscopic submucosal dissection for duodenal neoplasm without a papillary portion. *World J of Gastrointest Surg.* 2017;9(7):161. doi:10.4240/WJGS.V9.I7.161
9. Odagiri H, Yasunaga H. Complications following endoscopic submucosal dissection for gastric, esophageal, and colorectal cancer: a review of studies based on nationwide large-scale databases. *Ann Transl Med*. 2017;5(8):189-189. doi:10.21037/ATM.2017.02.12
10. Akahoshi K, Kubokawa M, Inamura K, Akahoshi K, Shiratsuchi Y, Tamura S. Current Challenge: Endoscopic Submucosal Dissection of Superficial Non-ampullary Duodenal Epithelial Tumors. *Curr Treat Options Oncol*. 2020;21(12). doi:10.1007/S11864-020-00796-Y
11. Thomas-Gibson S, Choy M, Dhillon AS. Education in practice: How to approach endoscopic mucosal resection (EMR). *Frontline Gastroenterol*. 2021;12(6):508. doi:10.1136/FLGASTRO-2019-101357
12. Navaneethan U, Hasan MK, Lourdusamy V, Zhu X, Hawes RH, Varadarajulu S. Efficacy and safety of endoscopic mucosal resection of non-ampullary duodenal polyps: a systematic review. *Endosc Int Open*. 2016;4(6):E699. doi:10.1055/S-0042-107069
13. Endoscopic treatment for duodenal non-papillary tumors and current status of complications (Stomach and intestines Vol.51 No.12) |. doi:doi.org/10.11477/mf.1403200770
14. Repici A, Hassan C, Vitetta E, et al. Safety of cold polypectomy for. *Endoscopy*. 2012;44(1):27-31. doi:10.1055/S-0031-1291387
15. Takeuchi Y, Mabe K, Shimodate Y, et al. Continuous anticoagulation and cold snare polypectomy versus heparin bridging and hot snare polypectomy in patients on anticoagulants with subcentimeter polyps. *Ann of Intern Med.* 2019;171(4):229-237. doi:10.7326/M19-0026
16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. Published 2009 Jul 21. doi:10.1136/bmj.b2535
17. Qumseya BJ. Quality assessment for systematic reviews and meta-analyses of cohort studies. *Gastrointest endosc.* 2021;93(2):486-494.e1. doi:10.1016/J.GIE.2020.10.007
18. Qumseya B, Qumsiyeh Y, Sarheed A, Rosasco R, Qumseya A. Barrett's Esophagus in Obese Patient Post-Roux-en-Y Gastric Bypass: a Systematic Review. *Obesity Surgery.* 2022;32(11):3513-3522. doi:10.1007/S11695-022-06272-W

19. Qumseya BJ, Qumsiyeh Y, Ponniah SA, et al. Barrett's esophagus after sleeve gastrectomy: a systematic review and meta-analysis. *Gastrointest endosc*. 2021;93(2):343-352.e2. doi:10.1016/J.GIE.2020.08.008
20. Beany A, Aguila EJ, Wawer A, et al. Hot versus cold snare endoscopic mucosal resection for nonampullary duodenal lesions. *Journal of Gastroenterology and Hepatology* 2022;37:205.
21. Trivedi M, Klapheke R, Youssef F, et al. Comparison of cold snare and hot snare polypectomy for the resection of sporadic nonampullary duodenal adenomas. *Gastrointest Endosc.* 2022;96(4):657-664.e2. doi:10.1016/j.gie.2022.05.007
22. Repici A, Capogreco A, Spadaccini M, et al. Cold versus hot EMR for large duodenal adenomas. *Gut*. 2022;71(9):1763-1765. doi:10.1136/gutjnl-2022-327171
23. Maruoka D, Matsumura T, Kasamatsu S, et al. Cold polypectomy for duodenal adenomas: a prospective clinical trial. *Endoscopy*. 2017;49(8):776-783. doi:10.1055/s-0043-107028
24. Okimoto K, Maruoka D, Matsumura T, et al. Long-term outcomes of cold snare polypectomy for superficial non-ampullary duodenal epithelial tumors. *J Gastroenterol Hepatol.* 2022;37(1):75-80. doi:10.1111/JGH.15666
25. Dang DT, Suresh S, Vance RB, et al. Outcomes of cold snare piecemeal EMR for nonampullary small-bowel adenomas larger than 1 cm: a retrospective study. *Gastrointest endosc.* 2022;95(6):1176-1182. doi:10.1016/J.GIE.2021.12.018
26. Okimoto K, Maruoka D, Matsumura T, et al. Short and long-term outcome of cold polypectomy for superficial non-ampullary duodenal epithelial tumors. *United European Gastroenterology Journal.* 2021;9(8):361. Doi:10.1002/ueg2.12144
27. Yoshida M, Yabuuchi Y, Kakushima N, et al. The incidence of non-ampullary duodenal cancer in Japan: The first analysis of a national cancer registry. *J Gastroenterol Hepatol* 2021;36:1216-1221.
28. Suwa T, Yoshida M, Ono H. Issues and Prospects of Current Endoscopic Treatment Strategy for Superficial Non-Ampullary Duodenal Epithelial Tumors. *Curr oncol.* 2022;29(10):6816-6825. doi:10.3390/CURRONCOL29100537
29. Probst A, Freund S, Neuhaus L, et al. Complication risk despite preventive endoscopic measures in patients undergoing endoscopic mucosal resection of large duodenal adenomas. *Endoscopy* 2020;52:847-855.
30. Amoyel M, Belle A, Dhooge M, et al. Outcomes of endoscopic mucosal resection for large superficial non-ampullary duodenal adenomas. *Sci Rep* 2022;12:14592.
31. Anderloni A, Jovani M, Hassan C, Repici A. Advances, problems, and complications of polypectomy. *Clin Exp Gastroenterol.* 2014;7(1):285. doi:10.2147/CEG.S43084
32. Valli P V., Mertens JC, Sonnenberg A, Bauerfeind P. Nonampullary Duodenal Adenomas Rarely Recur after Complete Endoscopic Resection: A Swiss Experience Including a Literature Review. *Digestion*. 2017;96(3):149-157. doi:10.1159/000479625
33. Rex DK, Anderson JC, Pohl H, et al. Cold versus hot snare resection with or without submucosal injection of 6- to 15-mm colorectal polyps: a randomized controlled trial. *Gastrointest Endosc* 2022;96:330-338.
34. Córdova H, Argüello L, Loras C, et al. Rate of adverse events of gastroduodenal snare polypectomy for non-flat polyp is low: A prospective and multicenter study. *World J Gastroenterol*. 2017;23(47):8405-8414. doi:10.3748/wjg.v23.i47.8405



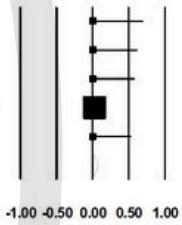


Study name	Odds ratio	Lower limit	Upper limit	p-Value	cold	hot	Relative weight
Beany 2022 (EMR)	0.109	0.006	2.041	0.138	0 / 21	6 / 36	31.99
Trivedi 2022	0.039	0.002	0.670	0.025	0 / 41	16 / 69	33.97
Repici 2022 (EMR)	0.072	0.004	1.233	0.069	0 / 33	17 / 101	34.04
	0.067	0.013	0.350	0.001			



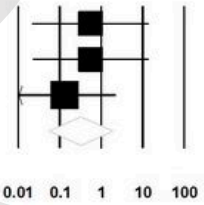
A

Study name	Event rate	Lower limit	Upper limit	p-Value	Total	Relative weight
Takizawa 2021	0.005	0.000	0.705	0.092	0 / 21	7.25
Daisuke 2017	0.003	0.000	0.624	0.072	0 / 30	7.26
Okimoto 2021	0.003	0.000	0.587	0.064	0 / 35	7.26
Dang 2022	0.026	0.004	0.161	0.000	1 / 39	70.96
Okimoto 2021c	0.002	0.000	0.530	0.055	0 / 44	7.27
	0.014	0.003	0.071	0.000		



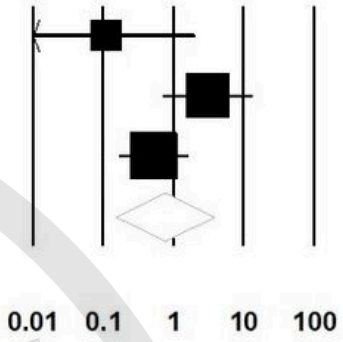
B

Study name	Odds ratio	Lower limit	Upper limit	p-Value	cold	hot	Relative weight
Beany 2022 (EMR)	0.55	0.02	14.13	0.718	0 / 21	1 / 36	30.33
Trivedi 2022	0.55	0.02	13.82	0.716	0 / 41	1 / 69	30.74
Repici 2022 (EMR)	0.13	0.01	2.28	0.163	0 / 33	10 / 101	38.93
	0.31	0.05	1.87	0.204			



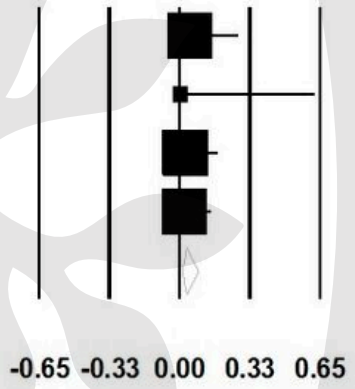
C

Study name	Odds ratio	Lower limit	Upper limit	p-Value	cold	hot	Relative weight
Beany 2022 (EMR)	0.11	0.01	2.04	0.138	0 / 21	6 / 36	19.47
Trivedi 2022	3.06	0.69	13.53	0.141	5 / 41	3 / 69	37.48
Repici 2022 (EMR)	0.53	0.17	1.66	0.273	4 / 33	21 / 101	43.05
	0.75	0.15	3.73	0.724			



A

Study name	Event rate	Lower limit	Upper limit	p-Value	Total	Relative weight
Takizawa 2021	0.048	0.007	0.271	0.003	1 / 21	31.74
Daisuke 2017	0.003	0.000	0.624	0.072	0 / 30	3.32
Okimoto 2021	0.029	0.004	0.177	0.001	1 / 35	32.37
Okimoto 2021c	0.023	0.003	0.144	0.000	1 / 44	32.57
	0.029	0.010	0.085	0.000		



B