Digestive and Liver Disease 55 (2023) 856–864

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Meta-Analysis

Comparative efficacy and safety of resection techniques for treating 6 to 20mm, nonpedunculated colorectal polyps: A systematic review and network meta-analysis[☆]

Georgios Tziatzios[a,1,*], Apostolis Papaefthymiou[b,1], Antonio Facciorusso[c], Ioannis S. Papanikolaou[a], Giulio Antonelli[d,e], Spadaccini Marco[f], Leonardo Frazzoni[g], Lorenzo Fuccio[g], Konstantina D. Paraskeva[h], Cesare Hassan[i], Alessandro Repici[i], Prateek Sharma[j,k], Douglas K Rex[l], Konstantinos Triantafyllou[a], Helmut Messmann[m], Paraskevas Gkolfakis[n]

[a] *Hepatogastroenterology Unit, Second Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, "Attikon" University General Hospital, Athens, Greece*
[b] *Department of Gastroenterology, University Hospital of Larissa, Larissa, Greece*
[c] *Gastroenterology Unit, Department of Medical Sciences, University of Foggia AOU, Ospedali Riunity Viale Pinto, Foggia, Italy*
[d] *Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, "Sapienza" University of Rome, Rome, Italy*
[e] *Gastroenterology and Digestive Endoscopy Unit, Ospedale dei Castelli Hospital, Ariccia, Rome, Italy*
[f] *Department of Endoscopy, Humanitas Research Hospital, IRCCS, Rozzano, Italy*
[g] *Gastroenterology Unit, Department of Medical and Surgical Sciences, IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico S Orsola-Malpighi, Bologna, Italy*
[h] *Department of Gastroenterology, "Konstantopoulio-Patision" General Hospital, Athens, Greece*
[i] *IRCCS Humanitas Research Hospital, Endoscopic Unit, Department of Gastroenterology, Milan, Italy*
[j] *Division of Gastroenterology & Hepatology, Department of Internal Medicine, University of Kansas School of Medicine, Kansas, United States*
[k] *Division of Gastroenterology, Veteran Affairs Medical Center, Kansas, Missouri, United States*
[l] *Division of Gastroenterology/Hepatology, Indiana University Hospital, Indianapolis, Indiana, United States*
[m] *Department of Gastroenterology, University Hospital Augsburg, Augsburg, Germany*
[n] *Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, CUB Erasme Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium*

ARTICLE INFO

Article history:
Received 2 August 2022
Accepted 13 October 2022
Available online 4 November 2022

Keywords:
Colorectal
Resection
Polyp
Meta-analysis
Colonoscopy
Polypectomy
Treatment

ABSTRACT

Introduction: Various endoscopic resection techniques have been proposed for the treatment of nonpedunculated colorectal polyps sized 6–20 mm, however the optimal technique still remains unclear.
Methods: A comprehensive literature review was conducted for randomized controlled trials (RCTs), investigating the efficacy of endoscopic treatments for the management of 6–20 mm nonpedunculated colorectal polyps. Primary outcomes were complete and en bloc resection rates and adverse event rate was the secondary. Effect size on outcomes is presented as risk ratio (RR; 95% confidence interval [CI]).
Results: Fourteen RCTs (5219 polypectomies) were included. Endoscopic mucosal resection(EMR) significantly outperformed cold snare polypectomy(CSP) in terms of complete [(RR 95%CI): 1.04(1.00–1.07)] and en bloc resection rate [RR:1.12(1.04–1.21)]. EMR was superior to hot snare polypectomy (HSP) [RR:1.04(1.00–1.08)] regarding complete resection, while underwater EMR (U-EMR) achieved significantly higher rate of en bloc resection compared to CSP [RR:1.15(1.01–1.30)]. EMR yielded the highest ranking for complete resection(SUCRA-score 0.81), followed by cold-snare EMR(CS-EMR,SUCRA-score 0.76). None of the modalities was different regarding adverse event rate compared to CSP, however EMR and CS-EMR resulted in fewer adverse events compared to HSP [RR:0.44(0.26–0.77) and 0.43(0.21–0.87),respectively].

☆ **Guarantor of the article:** Georgios Tziatzios

* Corresponding author at: Hepatogastroenterology Unit, Second Department of Internal Medicine – Propaedeutic Research Institute and Diabetes Center, Medical School, National and Kapodistrian University of Athens, "Attikon" University General Hospital, 1, Rimini Street, 124 62 Athens, Greece.
E-mail address: g_tziatzios@yahoo.gr (G. Tziatzios).

[1] Equal contribution.

https://doi.org/10.1016/j.dld.2022.10.011

Conclusion: EMR achieved the highest performance in resecting 6–20 mm nonpedunculated colorectal polyps, with this effect being consistent for polyps 6–9 and ≥10 mm; findings supported by very low quality of evidence.

1. Introduction

Endoscopic resection of colorectal adenomas during colonoscopy reduces both incidence and colorectal cancer-related mortality [1]. Beyond any doubt, cold snare polypectomy (CSP) is the optimal technique for removing diminutive polyps (size ≤ 5 mm), as endorsed in the current European Society of Gastrointestinal Endoscopy (ESGE) guidelines. Nonetheless, evidence on the efficacy of various endoscopic techniques available for the resection of lesions >5 mm remain scant [2]. Cold snaring achieves comparable efficacy to hot snaring for lesions ≤ 10 mm [3]; still, data evaluating its efficacy also for lesions 10–20 mm in size are limited [4]. On the other hand, hot snare polypectomy (HSP) may be considered alternatively to CSP, given its comparable efficacy in terms of complete resection and polyp retrieval rates [5], however both techniques are far from being perfect, namely due to the various incomplete polyp resection rates reported (10–61%) [6]. To make things even more conflicting, it remains unclear whether submucosal space expansion - the fundamental step in endoscopic mucosal resection (EMR) - indeed improves complete resection and at which cut-off polyp size it should be conducted [7,8]. To the best of our knowledge, there is only a single traditional pairwise meta-analysis on this issue showing similar complete resection rate between HSP and CSP, however the presence of heterogeneity and lack of evaluation of this specific setting for larger polyps are points that attract criticism [5]. In this context, we conducted a network meta-analysis that can address the comparative effectiveness of multiple interventions and synthesize data from individual randomized-controlled trials (RCTs), aiming to compare the efficacy and safety of different endoscopic techniques for the management of patients with 6–20 mm nonpedunculated colorectal polyps.

2. Materials and methods

2.1. Protocol registration

This systematic review and network meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) recommendations [9] (available at Supplementary Table 1) and an a priori established protocol available at the International Prospective Register of Systematic Reviews (PROSPERO; registration number **(CRD42022307165)**.

2.2. Selection criteria

The ***PICO*** statement was applied to define selection criteria; Patients: adults (age >18 years) undergoing colonoscopy for removal of 6–20 mm nonpedunculated colorectal polyp(s); Intervention: endoscopic techniques for non-pedunculated colorectal polyp removal including endoscopic mucosal resection (EMR), cold (CSP) or hot snare polypectomy (HSP), cold (C-EMR) or underwater EMR (U-EMR); Comparator: any of the aforementioned methods; Outcomes: primary outcomes was complete and *en bloc* resection rate, while the incidence of adverse events (i.e. bleeding, perforation) comprised the secondary outcome. Only prospective, parallel-group, randomized controlled trials, published in the English language were considered eligible for inclusion, while all other types of publications i.e. observational, feasibility or pilot studies, meta-analysis, editorials, narrative reviews, case reports/series were excluded.

2.3. Search strategy

A comprehensive computerized literature search was performed in PubMed/Medline database to identify eligible articles published from each database inception to March 2022. The search strategy (available at Supplementary Table 2) was performed including the free text terms “colorectal”, “polyp”, “endoscopic resection”, “random*” both as medical subject headings (MeSH) and free-text terms combined with the Boolean set operator ‘AND’. Two investigators (GT and AP) independently performed the search. Duplicates were removed followed by title and abstract evaluation of all search results for eligibility by three reviewers (GT, AP and PG). Predesigned electronic forms were used to assess eligibility for each selected article, while any disagreement was settled by discussion and consensus. Reference lists of all eligible studies and previous publications reporting on this issue were hand-searched as well, to identify potentially eligible studies missed during the first search. When multiple articles for a single population was available, we used the latest and more complete version. When data were not available, the corresponding author was reached via email to provide further information.

2.4. Data extraction and quality assessment

Data of interest from the individual studies were extracted within a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA) by three authors independently (GT, AP, PG). These included: first author‘s name, year of publication, country, number of centers, number of participants, age/sex of patients, characteristics of polyps (size and location), type of endoscopic technique used, number of polyps resected with each technique respectively, adenoma definition (i.e. conventional or sessile serrated adenoma - SSA/P), and adverse events including bleeding and perforation. Cochrane collaboration’s assessment tool was used to assess risk of bias within individual studies [10].

2.5. Data synthesis and statistical analysis

All outcomes were assessed by direct meta-analyses to estimate risk ratio (RR) and 95% confidence intervals (CI). Random-effects model (DerSimonian and Laird method) was used for analysis of outcomes to allow a more conservative estimate of the measured effect [11]. Heterogeneity was assessed using the I^2 statistic, with values exceeding 50% showing presence of significant heterogeneity, while small study effects were assessed by examining funnel plot asymmetry [12]. All direct analyses were carried out at Review Manager 5.3 (The Nordic Cochrane centre, The Cochrane Collaboration, Copenhagen, Denmark). Subsequently, network meta-analyses was undertaken both for primary and secondary outcomes, using a multivariate random-effects meta-regression [13]. A frequentist approach was implemented based on a random-effects consistency model to allow a point estimate from the network along with 95% CI from the frequency distribution of the estimate. One predefined sensitivity analyses was conducted to assess the robustness of findings for the primary outcome of the study, by repeating the network analysis dividing polyps into two different sizes (6–9 mm vs. ≥10 mm). In all analyses we undertook, the denominator was based on an intention-to-treat analysis as presented in each study. The surface under the cumulative ranking (SUCRA) curve method was used to estimate the relative ranking of the interventions for achieving the primary and secondary outcomes. SUCRA values range between 0, when a treatment is certainly the worst, and 1, when a treatment is certainly the optimal [14]. Consequently, higher scores result in higher ranking for successful polyp removal or AE prevention. R package netmeta (Foundation for Statistical Computing, Vienna, Austria) was used for all network meta-analysis. Data for single adverse events were estimated by included trials and pooled rates (95% CI) were reported.

2.6. Quality of evidence assessment

Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to evaluate the quality of evidence both from pairwise and network meta-analysis [15]. Inconsistency, risk of bias, indirectness, imprecision and risk of bias was judged by two researchers (GT and PG), independently for an overall quality as very low, low or moderate using the GRADEpro tool (GRADE Working Group) [16].

3. Results

3.1. Study selection

After initial identification of 744 relevant citations by the electronic literature search, 14 RCTs [17–30] finally met inclusion criteria and were enrolled in the systematic review and network meta-analysis. Overall, five different treatment strategies were evaluated (endoscopic mucosal resection – EMR, cold snare polypectomy – CSP, cold snare EMR – CS-EMR, hot snare polypectomy - HSP and underwater EMR – U-EMR, with a detailed overview of endoscopic resection techniques according to each study available at Supplementary Table 3). Studies' selection flowchart and available direct comparisons and network graph of trials are illustrated in Figs. 1 and 2, respectively.

3.2. Characteristics of included studies

Table 1 summarizes the basic characteristics of studies included in the analysis. Overall, the fourteen studies enrolled 3881 participants and analyzed outcomes from 5219 colorectal polyps' resections. Eleven RCTs were two-arm controlled trials, and five of them compared hot snare polypectomy vs. cold snare polypectomy [18,25,27-29], three hot snare polypectomy vs. endoscopic mucosal resection [17,19,26], one cold snare endoscopic mucosal resection vs. endoscopic mucosal resection [20], one cold snare polypectomy vs. endoscopic mucosal resection [21] and one underwater endoscopic mucosal resection vs. endoscopic mucosal resection [22]. There were also two 3-arm trials comparing cold snare polypectomy vs. cold snare endoscopic mucosal resection vs. endoscopic mucosal resection [23] and another comparing cold snare polypectomy vs. endoscopic mucosal resection vs. underwater endoscopic mucosal resection [24]. Finally, there was also a 4-arm trial that compared cold snare polypectomy vs. cold snare endoscopic mucosal resection vs. hot snare polypectomy vs. endoscopic mucosal resection [30]. Of note, 9 RCTs [18-21,25–29] provided data for polyps ≤10 mm. Complete resection rate and adverse events rate were reported in all studies, while *en bloc* resection (outcome definitions as provided in each study are summarized in Supplementary Table 3) could not be retrieved for three studies [20,26,27]. Patients' baseline characteristics (sex/age) and treatment-related features were evenly distributed between the active and comparator groups and across different trials (Table 1). Recruitment period ranged from 2013 to 2021 and the mean patient age was between 51.6 and 70 years.

3.3. Methodological quality and risk of bias

Overall risk of bias and quality at study-level assessments are presented in Supplementary Fig. 1A and B, respectively. Endoscopists were not blinded to intervention - implementation of a different resection technique – in none of the studies, rendering all of them susceptible to high risk of both performance and detection bias.

3.4. Primary outcomes

3.4.1. Complete resection rate

3.4.1.1. Pairwise meta-analysis. Regarding head-to-head comparisons between interventions under investigation, no statistically significant difference was found (Supplementary Fig. 2).

3.4.1.2. Network meta-analysis. Table 2 summarizes findings on the comparative efficacy of different methods and the comparative rates of adverse events. Among all available modalities, only EMR significantly outperformed CSP in terms of complete resection rate [RR 1.04 (1.00–1.07), Fig. 3A]. EMR was also found to be significantly superior to HSP [RR 1.04 (1.00–1.08), Table 2], when remaining methods were compared. Consequently, EMR achieved the highest ranking for complete resection (SUCRA-score 0.81), followed by CS-EMR (SUCRA-score 0.76, Table 3).

3.4.2. En bloc resection rate

3.4.2.3. Pairwise meta-analysis. Based on data from 2 RCTs [22,24] (476 polypectomies), U-EMR was significantly superior to EMR in terms of *en bloc* resection [RR 1.22; 1.09–1.36, $p = 0.0005$; Supplementary Fig. 3]. Regarding head-to-head comparisons between all the other interventions under investigation, no statistically significant difference was found (Supplementary Fig. 3).

3.4.2.4. Network meta-analysis. Regarding *en bloc* resection rate, EMR as well as U-EMR significantly outperformed CSP [RR 1.12 (1.04–1.21) and 1.15 (1.01–1.30), respectively, Fig. 3B]. However, comparisons among distinct adjunctive modalities, failed to demonstrate superiority of one method over the others (Table 2). Contrary to previous results, U-EMR was now the highest ranking modality for *en bloc* resection (SUCRA-score 0.86), followed by EMR (SUCRA-score 0.83, Table 3).

3.4.3. Analysis per polyp size

3.4.3.5. Polyps sized 6–9 mm. During the sensitivity analysis for polyps sized 6–9 mm, EMR outperformed both CSP and HSP [RR 1.08 (1.02–1.14), but not CS-EMR [RR 0.96 (0.8–1.05), Supplementary Table 4]. Treatment ranking was confirmed with EMR (SUCRA-score 0.93) having the higher probability to be the optimal treatment in this setting (Supplementary Table 5). As far as *en bloc* resection rate is concerned, none of the aforementioned treatments was found superior to others (Supplementary Table 4). Treatment ranking was the highest for EMR (SUCRA-score 0.96, Supplementary Table 5) for this subset of lesions.

3.4.4. Polyps sized ≥10 mm

When data from polyps ≥10 mm were analyzed, only HSP significantly outperformed CSP in terms of complete resection rate [RR 0.52 (0.41–0.66), Supplementary Table 6]. Of note, all other treatments significantly outperformed HSP, with RRs ranging from

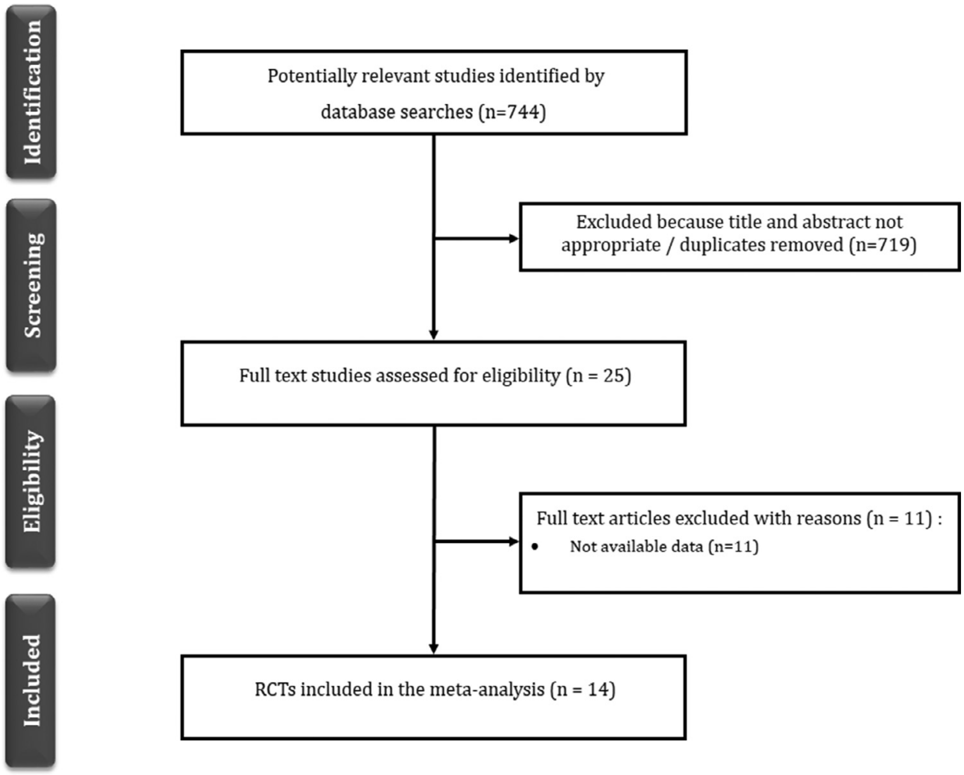

Fig. 1. Study flowchart.

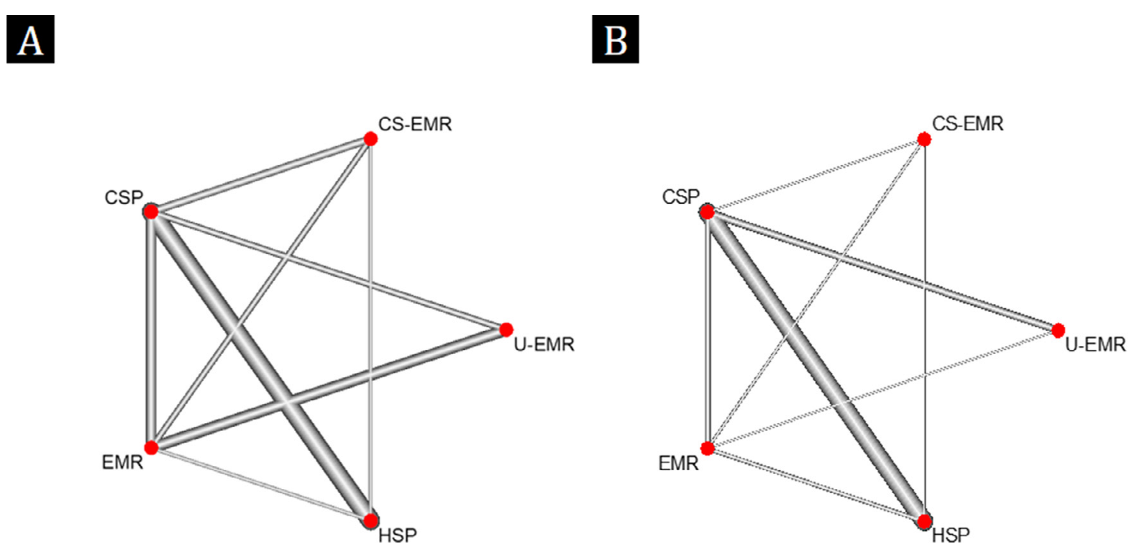

Fig. 2. Network graph of included trials for a) complete resection rate and (b) *en bloc* resection rate. Size of nodes and thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively.

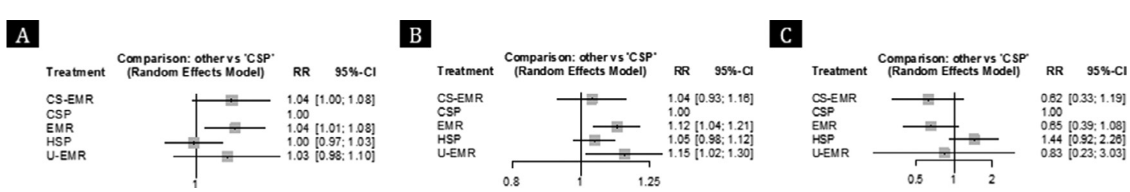

Fig. 3. Forest plots with estimates from network meta-analysis assessing (a) complete resection rate; (b) *en bloc* resection rate; (c) adverse event rate. Cold snare polypectomy was used as reference.

Table 1
Characteristics of included studies.

N	Author, year	Country	Study design	Recruitment period	Pts	Max polyp diameter (mm)	Resection techniques	Polyps resected	Age [mean ± SD, median (range)]	Sex, female; n (%)	Lesion Size [mean ± SD, median (range)]	Adverse Events
1	Horiuchi et al., 2016 [17]	Japan	Single center parallel	2013–2014	104	25	EMR	51	68.3 ± 9.8	41 (39.4)	14.8 ± 4.1	0
							HSP	51	65.9 ± 1.1		14.7 ± 4.5	0
2	Kawamura et al., 2017 [18]	Japan	Multicentre, parallel	2015–2016	476	9	HSP	129	66	155 (32.6)	7 (6–9)	29
							CSP	127	65.3		7 (6–9)	16
3	Kim et al., 2018 [19]	Korea	Single center parallel	2014–2015	269	9	HSP	172	64±10	104 (38.7)	6.2 (1.3)	9
							EMR	181	64.3 ± 10.1		6.3 (1.4)	1
4	Papastergiou et al., 2017 [20]	Greece	Multicentre, parallel	2016	155	10	CS-EMR	83	63.6 ± 10.6	64 (41.3)	8.2 (1.6)	3
							EMR	81			8.3 (1.4)	1
5	Zhang et al., 2017 [21]	China	Single center parallel	2014–2016	358	9	CSP	267	64.9 ± 8.7	161 (45.0)	7.4 (± 1.4)	5
							EMR	258			7.7 (± 1.5)	3
6	Yamashina et al., 2019 [22]	Japan	Multicentre, parallel	2016–2017	210	20	EMR	102	68 (42–95)	71 (33.8)	13.5 (7–25)	2
							U-EMR	108	70 (43–86)		14 (7–25)	3
7	Li et al., 2020 [23]	China	Single center parallel	2017–2019	404	20	CSP	244	63 ± 14.4	168 (41.6)	11.95 ± 3.35	27
							CS-EMR	252	51.77 ± 14.5		12.03 ± 3.36	13
							EMR	267	51.59 ± 14.4		12.22± 3.77	14
8	Yen et al., 2019 [24]	USA	Single center parallel	2016–2018	255	19	CSP	164	n/a	n/a	6–9	1
							EMR	34			10–19	1
							U-EMR	232			6–19	2
9	Ito et al., 2021 [25]	Japan	Single center cross-over	2015–2018	119	9	CSP	175	66.8 ± 12.4	41 (34.5)	7 (6–9)	3
							HSP	157	66.9 ± 9.8		6 (6–9)	3
10	Kim et al., 2020 [26]	Korea	Single center parallel	2014–2017	272	10	HSP	167	62.8 ± 10.7	144 (40.4)	7.1 (1.5)	18
							EMR	155	63±10.8		7.2 (1.6)	12
11	Varytimiadis et al., 2021 [27]	Greece	Single center parallel	2015–2018	111	9	CSP	39	61.2 ± 10	41 (36.9)	6.4 ± 0.7	n/a
							HSP	45			7.3 ± 0.9	
12	De Benito Sanz et al., 2019 [28]	Spain	Multicenter cross-over	2019	488	7	CSP	394	64.6 (56.7–70.7)	169 (34.6)	6 (5–7)	58
							HSP	397			6 (5–7)	75
13	Pedersen et al., 2022 [29]	Norway, Denmark, Poland	Multicentre, parallel	2015–2020	425	9	CSP	318	n/a	n/a	n/a	n/a
							HSP	283				
14	Rex et al., 2022 [30]	USA	Multicentre, parallel	2018–2021	235	15	CSP	68	66.2(9.9)	89 (37.9)	9.4 ± 3.1	0
							CS-EMR	82	65(8)		9.5 ± 2.8	1
							HSP	71	66.3(8)		10.1 ± 2.9	2
							EMR	65	67(8.4)		10.0 ± 3.1	4

CSP, cold snare polypectomy; CS-EMR, cold snare EMR; EMR, endoscopic mucosal resection; HSP, hot snare polypectomy; SD, standard deviation; U-EMR, underwater EMR.

1.33 to 2.75 (Supplementary Table 6). Finally, the treatment ranking confirmed that EMR along with CS-EMR were the most effective and safest modalities for this size of polyps (SUCRA-score 0.67 and 0.66, respectively; Supplementary Table 7). A similar analysis regarding *en bloc* resection was not feasible due to absence of data.

3.5. Secondary outcomes - Adverse event rate

All studies but one [29], provided data regarding adverse events with their definitions being homogenous and including intra-procedural/delayed bleeding, perforation and post-polypectomy syndrome. Supplementary Table 8 presents in detail the main adverse events reported in the included RCTs, while the pooled rates of adverse events (overall, bleeding and perforation) per therapeutic modality are summarized in Supplementary Table 9.

3.6. Pairwise meta-analysis

According to data from 4 RCTs [18,25,28,30] (1301 polypectomies), CSP resulted in significantly fewer overall adverse events compared to HSP (RR 0.78; 0.60–1.01, Supplementary Fig. 4), with absence of heterogeneity (I^2=0%). No difference between HSP and EMR was found based on 4 RCTs [17,19,26,30] (847 polypectomies) (RR 1.87, 0.62–5.57), while all remaining direct comparisons did not detect statistically significant differences (Supplementary Fig. 4).

Table 2
GRADE Summary of Findings reporting the comparative efficacy of different methods for removal of colorectal polyps and the comparative rates of adverse events*.

	Complete resection		En bloc resection		Adverse events rate	
	Risk Ratio (95% CI)	Quality of Evidence	Risk Ratio (95% CI)	Quality of Evidence	Risk Ratio (95% CI)	Quality of Evidence
All treatments vs. CSP						
HSP	0.99 (0.96–1.03)	Very Low due to indirectness, inconsistency and risk of bias in literature	1.04 (0.97–1.12)	Very Low due to indirectness, inconsistency and risk of bias in literature	1.44 (0.91–2.26)	Low due to indirectness and risk of bias in literature
EMR	**1.04 (1.00–1.07)**	Very Low due to indirectness, inconsistency and risk of bias in literature	**1.12 (1.04–1.21)**	Very Low due to indirectness, inconsistency and risk of bias in literature	0.64 (0.38–1.07)	Very Low due to indirectness, inconsistency and risk of bias in literature
CS-EMR	1.03 (0.99–1.08)	Very Low due to indirectness, inconsistency and risk of bias in literature	1.03 (0.92–1.16)	Very Low due to indirectness, inconsistency and risk of bias in literature	0.62 (0.32–1.18)	Very Low due to indirectness, inconsistency and risk of bias in literature
U-EMR	1.03 (0.97–1.09)	Very Low due to indirectness, inconsistency and risk of bias in literature	**1.15 (1.01–1.30)**	Low due to indirectness and risk of bias in literature	0.83 (0.22–3.03)	Low due to indirectness and risk of bias in literature
vs. HSP						
EMR	**1.04 (1.00–1.08)**	Very Low due to indirectness, inconsistency and risk of bias in literature	1.07 (0.98–1.16)	Very Low due to indirectness, inconsistency and risk of bias in literature	**0.44 (0.26–0.77)**	Very Low due to indirectness, inconsistency and risk of bias in literature
CS-EMR	1.04 (0.99–1.09)	Very Low due to indirectness, inconsistency and risk of bias in literature	0.99 (0.87–1.11)	Very Low due to indirectness, inconsistency and risk of bias in literature	**0.43 (0.21–0.87)**	Very Low due to indirectness, inconsistency and risk of bias in literature
U-EMR	1.03 (0.97–1.04)	Very Low due to indirectness, inconsistency and risk of bias in literature	1.09 (0.95–1.26)	Very Low due to indirectness, inconsistency and risk of bias in literature	0.57 (0.15–2.17)	Very Low due to indirectness, inconsistency and risk of bias in literature
vs. EMR						
CS-EMR	0.99 (0.95–1.03)	Very Low due to indirectness, inconsistency and risk of bias in literature	0.92 (0.82–1.03)	Very Low due to indirectness, inconsistency and risk of bias in literature	0.96 (0.50–1.81)	Low due to indirectness and risk of bias in literature
U-EMR	0.99 (0.93–1.04)	Very Low due to indirectness, inconsistency and risk of bias in literature	1.02 (0.90–1.15)	Very Low due to indirectness, inconsistency and risk of bias in literature	1.28 (0.36–4.48)	Low due to indirectness and risk of bias in literature
vs. CS-EMR						
U-EMR	0.99 (0.93 –1.06)	Very Low due to indirectness, inconsistency and risk of bias in literature	1.11 (0.94–1.30)	Very Low due to indirectness, inconsistency and risk of bias in literature	1.33 (0.33 –5.29)	Very Low due to indirectness, inconsistency and risk of bias in literature

* Quality of the evidence was rated based on GRADE methodology. RCTs of direct comparison were rated down for presence of any of the following factors – risk of bias in literature, inconsistency, indirectness, imprecision, and publication bias. Quality of indirect estimates was initially derived from the lowest quality of first-order loops for direct estimates contributing to the indirect estimates. Quality of the network meta-analysis was derived from quality of combination of direct and indirect estimates and transitivity of trials. Risk ratios reaching the significance threshold are reported in bold. CSP, cold snare polypectomy; CS-EMR, cold snare EMR; EMR, endoscopic mucosal resection; HSP, hot snare polypectomy; SD, standard deviation; U-EMR, underwater EMR.

Table 3
SUCRA score ranking for complete, en bloc and adverse event rate.

Complete resection		En bloc resection		Adverse event rate	
EMR	0.81	U-EMR	0.86	CS-EMR	0.77
CS-EMR	0.76	EMR	0.83	EMR	0.77
U-EMR	0.51	CS-EMR	0.50	U-EMR	0.53
CSP	0.23	HSP	0.31	CSP	0.26
HSP	0.17	CSP	0.11	HSP	0.15

CSP, cold snare polypectomy; CS-EMR, cold snare EMR; EMR, endoscopic mucosal resection; HSP, hot snare polypectomy; SD, standard deviation; U-EMR, underwater EMR.

3.7. Network meta-analysis and quality of evidence

On network meta-analysis, none of the tested therapeutic modalities was found to significantly differ in terms of adverse events compared to CSP (Fig. 3C). However, both EMR and CS-EMR were associated to significantly fewer adverse event rates compared to HSP [RR 0.44 (0.26–0.77) and 0.43 (0.21–0.87), respectively, Table 2]. Notably, EMR and CS-EMR were deemed equivalent as both reached the highest ranking (SUCRA-score 0.77), with HSP not only showing the poorest value overall (SUCRA-score 0.15, Table 3), but with this effect being consistent for polyps 6–9 mm [RR 1.37 (1.02–1.84), Supplementary Table 3]. The quality of evidence was judged as very low due to indirectness, inconsistency and risk of bias in literature.

3.8. Small study effects, network coherence, and sensitivity analysis

No evidence of small study effects according to funnel plot asymmetry (data not shown) was found, while there was no significant difference between direct and indirect estimates in closed loops that allowed assessment of network coherence.

4. Discussion

Several endoscopic methods are currently available in clinical practice for the treatment of nonpedunculated colorectal polyps sized 6–20 mm, but there are limited data on their overall and comparative efficacy. Although current guidelines advocate the potential of these methods for improving polypectomy outcomes in this subgroup of lesions, they caution that definite recommendations on the superiority of one method over another cannot be made [2]. In this context, our network meta-analysis and critical evidence synthesis - implementing GRADE criteria to appraise the quality of evidence - provides a handful of valuable insights for the treatment of patients with lesions of this size, aiming to optimize polypectomy outcomes along with a favorable patient safety profile in everyday clinical practice.

The main result was that EMR involving the traditional “*inject and cut*” method was associated with significant improvement, compared to cold snare polypectomy in terms of complete as well as *en bloc* resection rates and is also safer to perform compared to hot snare polypectomy; however, despite the presence of a clear-cut benefit, the overall quality of evidence supporting this notion was deemed very low. Hence, EMR ranked highest in increasing the success rate of complete resection (SUCRA-score 0.81) and second to U-EMR for *en bloc* resection (SUCRA-score 0.83). The advent of EMR almost three decades ago revolutionized colorectal polyps’ removal, establishing its pivotal role as the first line modality for removing large, flat or laterally spreading adenomas [2,7]. Still, its inverse proportional efficacy in terms of complete resection to the size of the polyp, ranging from 2 to 30% for polyps larger than 10 mm and the high rate of recurrence, reaching as high as 20% especially after piecemeal EMR, represent the method’s principal caveats [31–33]. The higher complete resection rate, achieved using EMR compared to CSP noted in our analysis, might be attributed to a number of potential reasons: first, submucosal injection beneath the lesions optimizes visualization of the lesion’s delineation margin before resection, feature that is, perhaps, of paramount importance for complete resection; second, successful elevation prevents lesion slippage from the snare, and third, in the case of residual lesion escaping snare entrapment, the electrical energy applied can improve the rate of complete resection [7,8]. Finally, the role of a dedicated snare could be also speculated. Traditional snares are more likely to fail cutting through captured tissue when used for cold resection, with each attempt for re-snaring leading to incomplete resection [34,35]. The finding that underwater EMR outperforms the conventional method in terms of *en bloc* resection rate is not novel and it is in line with that reported in a recent pairwise meta-analysis, where underwater EMR was advantageous compared to EMR, particularly for resection of large (≥20 mm) polyps [36]. When water fills the colon, it maintains both the mucosa and sub mucosa layers contracted, preventing large lesions to further extend but also allowing standard sized snares to grasp large lesions. Contrariwise, submucosal injection may undermine the resection outcome due to uneven submucosal fluid accumulation beneath the lesion impeding snare capture, while excessive submucosal expansion can lead to lesion concealment, difficulty in scope maneuverability or lesion slippage from snare [36]. U-EMR showed on the other hand, equivalent efficacy in terms of complete resection compared to the other methods evaluated, perhaps due to the fact that all studies were conducted in high-volume, referral centers by expert endoscopists that already achieve high complete resection rates with conventional resection methods. Still, this finding may regarded significant as it supports the method’s feasibility in any given setting.

Second, on comparative evaluation among different approaches for nonpedunculated polyps sized 6–9 mm, EMR was demonstrated to be the only therapeutic option that consistently improved polypectomy outcomes for polyps 6–9 mm, being probably superior to other interventions. These polyps represent the predominant type of colorectal adenomas and are generally considered easy to remove during colonoscopy by means of cold snare polypectomy, given its well-known advantages including cost-neutrality, availability and “operator-friendly” character [37,38]. Still, performance of CSP remains somewhat suboptimal as data suggest that incomplete resection of these lesions is relatively common (8.5%) in daily clinical practice [21]. More ominous is perhaps the fact that these lesions may harbor a considerably high the rate of advanced adenoma (6.6% - 35.2%), finding that could eventually lead to interval cancers [39]. In this regard, EMR could form a handy alternative for endoscopists for this particular subset of polyps. Still, before one could claim EMR as the resection method of choice, there are several issues to be addressed. EMR may be still not available in every clinical practice setting worldwide, while its efficacy might vary according to each endoscopist‘s technical proficiency. Moreover, the additional financial burden for the healthcare system posed by the method, along with its environmentally unfriendly character - due to the self-evident production of more plastic waste - and inefficiency associated versus cold snaring, are also factors that cannot be neglected [7]. Hence, further research is warranted to delineate the relationship between the baseline adenoma size and improvement in polypectomy outcomes with each resection approach.

Another point that deserves attention is the fact that the tested interventions resulted in similar risk of overall adverse events with this finding being consistent in direct or in indirect comparisons, and only HSP showing the poorest value (SUCRA-score 0.15) in the ranking concerning this particular outcome. Among the reported adverse events, bleeding was the most common, which in most cases was self-limited or occasionally could be controlled by endoscopic means (snare tip soft coagulation and/or by haemostatic clip placement). However, this finding should be interpreted cautiously as adverse events were grouped and analyzed as a total; thus, no separate estimates for each one is available.

The superiority of EMR over CSP - with very low quality of evidence - for polyps 6 to 9 mm polyps as well as for larger lesions is the most clinical implication of our study for everyday clinical practice. Despite that, one should be prudent before considering extrapolating this finding uniformly in each case, as differences between the two groups may have a different practical aspect. Cold snaring has already become the most widely used method for lesions 6–9 mm, that represent the most common group of polyps, with decreasing prevalence for each increasing size category. On the other hand, practice is probably much more mixed for polyps ≥10 mm, where EMR - the optimal method according to our analysis - may still be a technically demanding procedure when resecting a lesion. Moreover, we should also be cautious when interpreting the superiority of any method, as the quality of the resection itself cannot be controlled. Some endoscopists might perform better at one technique than another and some might be better at performing a specific technique than the endoscopists in a different study performing the same technique. Taking these observations into account, one might conclude that the principal clinical implication of our analysis suggests a greater tendency of EMR use in the ≥10 mm group but not in the 6–9 mm group, where observed differences may actually fall short to change everyday practice. “Gray” areas deserving more data are the efficacy of each method in the resection of sessile serrated polyps and lesions with difficultly in access i.e. ileo- cecal valve, appendiceal orifice, or resected previously incompletely. Hence, future adequately powered, head-to-head randomized studies should investigate factors (histology, location, endoscopist’s expertise level) that will allow identification of the heterogeneity source of treatment effect and guide the optimal approach.

Several limitations related to both the network design of our study and the design of the individual studies that merit further discussion are to be noted. First, network meta-analyses data are subject to misinterpretation due to the limited available head-to-head comparisons for certain outcomes. In view of this, the rigorous methodology applied for the analysis permits us to draw reliable conclusions. Second, all included studies were unblinded RCTs, a bias commonly encountered when endoscopic devices and techniques are investigated, where blinding of the operator is not possible, constituting them susceptible to performance and detection biases. Thus, a decision not to include studies published as abstracts - with additional risk of bias - along with a strict critical appraisal of the overall quality of evidence using the standardized GRADE methodology was made to harmonize this. Third, network meta-analyses may also lead to misinterpretation due to conceptual heterogeneity, derived from existing differences in participants, interventions, co-interventions/background treatment application, and outcome assessment i.e. complete resection definition was neither uniform nor conducted according to a common established biopsy protocol among the studies included, limiting the comparability of trials. Fourth, it was not possible to adjust our analysis for center-, endoscopist- (i.e. as endoscopist‘s level of expertise, resection time) or lesion-related data (a per histology analysis for serrated lesions), as we did not have access to the individual data sets. Finally, one might consider that some techniques as the U-EMR have not been incorporated as mainstream technique in daily practice, yet.

In conclusion, this is the first systematic review and network meta-analysis to assess efficacy of available methods for resecting non-pedunculated colorectal polyps sized 6–20 mm. Based on a very low level of evidence according to the GRADE methodology, EMR seems to have an advantage over other endoscopy resection techniques, such as CSP or HSP, for improving the principal polypectomy outcomes. Larger pragmatic trials comparing different techniques and estimating their impact on reducing risk of interval colorectal cancer are warranted.

Declaration of Competing Interest

None declared.

Contributors

P Gkolfakis conceived the idea, G Tziatzios, A Papaefthymiou and P Gkolfakis acquired the data, performed the meta-analysis, drafted and finally approved the manuscript; A Facciorusso performed the meta-analysis, drafted and finally approved the manuscript; I S. Papanikolaou, G Antonelli, M Spadaccini, L Frazzoni, L Fuccio, K D. Paraskeva, C Hassan, A Repici, P Sharma, D K Rex, K Triantafyllou, H Messmann revised the draft critically for important intellectual content and finally approved the manuscript.

Funding statement

None received.

Acknowledgments

We thank Dr IB Pedersen for providing raw data from their study

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.10.011.

References

[1] Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687–96.
[2] Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy 2017;49:270–97.
[3] Repici A, Hassan C, Vitetta E, et al. Safety of cold polypectomy for <10 mm polyps at colonoscopy: a prospective multicenter study. Endoscopy 2012;44:27–31.
[4] Djinbachian R, Iratni R, Durand M, et al. Rates of incomplete resection of 1- to 20-mm colorectal polyps: a systematic review and meta-analysis. Gastroenterology 2020;159:904–14 e912.
[5] Shinozaki S, Kobayashi Y, Hayashi Y, et al. Efficacy and safety of cold versus hot snare polypectomy for resecting small colorectal polyps: Systematic review and meta-analysis. Dig Endosc 2018;30:592–9.
[6] Farrar WD, Sawhney MS, Nelson DB, et al. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol 2006;4:1259–64.
[7] Kandel P, Wallace MB. Colorectal endoscopic mucosal resection (EMR). Best Pract Res Clin Gastroenterol 2017;31:455–71.
[8] Tziatzios G, Gkolfakis P, Papadopoulos V, et al. Modified endoscopic mucosal resection techniques for treating precancerous colorectal lesions. Ann Gastroenterol 2021;34:757–69.
[9] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.
[10] Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from http://handbook.cochrane.org 2011, DOI:.
[11] DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45:139–45.
[12] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta–analyses. BMJ 2003;327:557–60.
[13] Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making 2013;33:607–17.
[14] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–71.

[15] Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta–analysis. Bmj 2014;349:g5630.
[16] Schünemann H. B.J, Guyatt G., Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations (Updated October 2013). The GRADE Working Group, 2013 https://gdtgradeproorg/app/handbook/handbookhtml [Accessed Jan 28, 2019] 2013, DOI:
[17] Horiuchi A, Makino T, Kajiyama M, et al. Comparison between endoscopic mucosal resection and hot snare resection of large nonpedunculated colorectal polyps: a randomized trial. Endoscopy 2016;48:646–51.
[18] Kawamura T, Takeuchi Y, Asai S, et al. A comparison of the resection rate for cold and hot snare polypectomy for 4-9 mm colorectal polyps: a multicentre randomised controlled trial (CRESCENT study). Gut 2018;67:1950–7.
[19] Kim H-S, Jung HY, Park HJ, et al. Hot snare polypectomy with or without saline solution/epinephrine lift for the complete resection of small colorectal polyps. Gastrointest Endosc 2018;87:1539–47.
[20] Papastergiou V, Paraskeva KD, Fragaki M, et al. Cold versus hot endoscopic mucosal resection for nonpedunculated colorectal polyps sized 6-10 mm: a randomized trial. Endoscopy 2018;50:403–11.
[21] Zhang Q, Gao P, Han B, et al. Polypectomy for complete endoscopic resection of small colorectal polyps. Gastrointest Endosc 2018;87:733–40.
[22] Yamashina T, Uedo N, Akasaka T, et al. Comparison of underwater vs conventional endoscopic mucosal resection of intermediate-size colorectal polyps. Gastroenterology 2019;157:451–61 e452.
[23] Li D, Wang W, Xie J, et al. Efficacy and safety of three different endoscopic methods in treatment of 6-20 mm colorectal polyps. Scand J Gastroenterol 2020;55:362–70.
[24] Yen AW, Leung JW, Wilson MD, et al. Underwater versus conventional endoscopic resection of nondiminutive nonpedunculated colorectal lesions: a prospective randomized controlled trial (with video). Gastrointest Endosc 2020;91:643–54 e642.
[25] Ito T, Takahashi K, Tanabe H, et al. Safety and efficacy of cold snare polypectomy for small colorectal polyps: A prospective randomized control trial and one-year follow-up study. Medicine 2021;100:e26296.
[26] Kim S-J, Lee B-I, Jung ES, et al. Hot snare polypectomy versus endoscopic mucosal resection for small colorectal polyps: a randomized controlled trial. Surg Endosc 2021;35:5096–103.
[27] Varytimiadis L, Viazis N, Gkolfakis P, et al. Cold snare polypectomy vs. hot snare polypectomy vs. argon plasma coagulation for small (5-9 mm) left-sided colorectal polyps: a prospective randomized trial. Eur J Gastroenterol Hepatol 2021;33:e909–15.
[28] de Benito Sanz M, Hernandez L, Garcia Martinez MI, et al. Efficacy and safety of cold versus hot snare polypectomy for small (5-9 mm) colorectal polyps: a multicenter randomized controlled trial. Endoscopy 2022;54:35–44.
[29] Pedersen IB, Rawa-Golebiewska A, Calderwood AH, et al. Complete polyp resection with cold snare versus hot snare polypectomy for polyps of 4-9 mm: a randomized controlled trial. Endoscopy 2022. doi:10.1055/a-1734-7952.
[30] Rex DK, Anderson JC, Pohl H, et al. Cold versus hot snare resection with or without submucosal injection of 6-15 mm colorectal polyps: a randomized controlled trial. Gastrointest Endosc 2022. doi:10.1016/j.gie.2022.03.006.
[31] Hurlstone DP, Sanders DS, Cross SS, et al. Colonoscopic resection of lateral spreading tumours: a prospective analysis of endoscopic mucosal resection. Gut 2004;53:1334–9.
[32] Belderbos TD, Leenders M, Moons LM, et al. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. Endoscopy 2014;46:388–402.
[33] Komeda Y, Watanabe T, Sakurai T, et al. Risk factors for local recurrence and appropriate surveillance interval after endoscopic resection. World J Gastroenterol 2019;25:1502–12.
[34] Horiuchi A, Hosoi K, Kajiyama M, et al. Prospective, randomized comparison of 2 methods of cold snare polypectomy for small colorectal polyps. Gastrointest Endosc 2015;82:686–92.
[35] Hewett DG. Cold snare polypectomy: optimizing technique and technology (with videos). Gastrointest Endosc 2015;82:693–6.
[36] Tziatzios G, Gkolfakis P, Triantafyllou K, et al. Higher rate of en bloc resection with underwater than conventional endoscopic mucosal resection: A meta–analysis. Dig Liver Dis 2021;53:958–64.
[37] Rex DK. Narrow-band imaging without optical magnification for histologic analysis of colorectal polyps. Gastroenterology 2009;136:1174–81.
[38] Tutticci NJ, Kheir AO, Hewett DG. The Cold Revolution: How Far Can It Go? Gastrointest Endosc Clin N Am 2019;29:721–36.
[39] Lieberman D, Moravec M, Holub J, et al. Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. Gastroenterology 2008;135:1100–5.