Effectiveness and safety of the different endoscopic resection methods for 10- to 20-mm nonpedunculated colorectal polyps: A systematic review and pooled analysis

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Abstract

Background: We performed a systematic review and pooled analysis to assess the effectiveness and safety of different endoscopic resection methods for 10- to 20-mm nonpedunculated colorectal polyps.

Methods: Articles in PubMed, EMBASE, and the Cochrane Library related to the common endoscopic treatment of 10- to 20-mm nonpedunculated polyps published as of April 2020 were searched. Primary outcomes were the R0 resection rate and en bloc resection rate. Secondary outcomes were safety and the recurrence rate. Meta-regression and subgroup analysis were also performed.

Results: A total of 36 studies involving 3212 polyps were included in the final analysis. Overall, the effectiveness of resection methods with a submucosal uplifting effect, including endoscopic mucosal resection (EMR), cold EMR and underwater EMR (UEMR), was better than that of methods without a nonsubmucosal uplifting effect [R0 resection rate, 90% (95% confidence interval (CI) 0.81–0.94, $I^2 = 84\%$) vs 82% (95% CI 0.78–0.85, $I^2 = 0\%$); en bloc resection rate 85% (95% CI 0.79–0.91, $I^2 = 83\%$) vs 74% (95% CI 0.47–0.94, $I^2 = 94\%$)]. Regarding safety, the pooled data showed that hot resection [hot snare polypectomy, UEMR and EMR] had a higher risk of intraprocedural bleeding than cold resection [3% (95% CI 0.01–0.05, $I^2 = 68\%$) vs 0% (95% CI 0–0.01, $I^2 = 0\%$)], while the incidences of delayed bleeding, perforation and post-polypectomy syndrome were all low.

Conclusions: Methods with submucosal uplifting effects are more effective than those without for resecting 10- to 20-mm nonpedunculated colorectal polyps, and cold EMR is associated with a lower risk of intraprocedural bleeding than other methods. Additional research is needed to verify the advantages of these methods, especially cold EMR.

Keywords: Colonic polyps, colonoscopy, endoscopic polypectomy, meta-analysis, systematic review

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INTRODUCTION

Colorectal cancer (CRC) evolves from colorectal polyps and other lesions through different molecular pathways.[1] Due to the development and promotion of endoscopic techniques as well as increasing awareness of endoscopic examination for the prevention and treatment of CRC,

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polyps <10 mm in size account for 90% of all colorectal polyps detected.[2] However, diminutive and small polyps are rarely highly dysplastic, while large polyps, especially nonpedunculated polyps, tend to be high-grade neoplasias and have a high risk of being cancerous.[3,4] Therefore, the removal of these lesions is of great significance for preventing CRC and reducing the related mortality.

At present, for the endoscopic resection of lesions without signs of submucosal invasion, cold snare polypectomy (CSP) is recommended for lesions smaller than 10 mm, and hot snare polypectomy (HSP) is suggested for pedunculated lesions larger than 10 mm. Furthermore, endoscopic mucosal resection (EMR) is recommended for nonpedunculated lesions larger than 20 mm according to the European Society of Gastrointestinal Endoscopy clinical guidelines and by the US Multi-Society Task Force.[5,6] However, there is no high-quality evidence for the optimal resection of 10- to 20-mm (intermediate-size) nonpedunculated lesions or specific recommendations for such resection in recent guidelines. It remains unclear whether hot or cold resection is preferable, and if submucosal injection ought to be performed before resection. The main methods in use include EMR, cold EMR, underwater EMR (UEMR), CSP and HSP.[7,8]

Ever since colonoscopy was introduced to treat colorectal diseases, many clinical studies on the resection of colorectal lesions have been published, but few studies have focused mainly on 10- to 20-mm polyps. Moreover, the sample size of some studies is not sufficient, and data on the effectiveness and safety of different resection methods for intermediate-size polyps have never been analysed or systematically reviewed.

Therefore, we performed this study to compare the results of different resection methods, with a focus on their effectiveness and safety outcomes.

MATERIALS AND METHODS

We performed this study based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations, and the study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO, www.crd.york.ac.uk/prospero/) in July (registration number: CRD42020180152).

Inclusion and exclusion criteria

We formulated the literature eligibility criteria according to PICO principles: P: patients who had undergone colonoscopy and had 10- to 20-mm nonpedunculated polyps; I and C: patients who had undergone colonoscopy via one of various common resection methods; and O: effectiveness (i.e. R0 resection rate, en bloc resection rate) and (or) safety (i.e. intraprocedural bleeding rate, delayed bleeding rate, perforation rate, and postpolypectomy syndrome rate). Retrospective and prospective studies including valid data were considered. Case reports and reviews were excluded.

Search strategy and selection process

We comprehensively searched the literature using PubMed, EMBASE, and the Cochrane Library (up to 15 April 2020) for studies related to the endoscopic treatment of nonpedunculated polyps. Electronic searches were conducted by two investigators (XY and ZZ) independently; the EMBASE search strategy is presented in Supplementary Table 1. After the removal of duplicate literature using an embedded Endnote (Endnote X9) function, the titles and abstracts were first screened according to the eligibility criteria, and then the full texts of the preliminarily screened articles were read to determine their further eligibility.

Data extraction

The eligible data were extracted by the two reviewers (JX and YZ) independently and recorded in a standard format in a Microsoft Excel spreadsheet. The extracted data included the type of study, name of the first author, year of publication, country of origin, method of lesion resection, number of complete resections, number of en bloc resections, number of cases of intraprocedural bleeding, number of cases of delayed bleeding, number of occurrences of perforation, number of occurrences of postpolypectomy syndrome, management of adverse events, duration of follow-up, and number of recurrences. We also extracted the number of centres, number of lesions, type and size of lesions, type of endoscope, type of snare, type and energy of electrocoagulation generator device, and number and experience of endoscopic operators. Any disagreement was settled by discussion with the arbitrator (LX).

Outcome and quality assessment

The primary outcomes were the R0 resection rate and en bloc resection rate. R0 resection was defined as complete resection with a histologically confirmed negative resection margin and no residual neoplastic tissue at any point on the horizontal or vertical cut margins, and en bloc resection was defined as endoscopically assessed removal of the lesion in one piece. Secondary outcomes were the rate of procedure-related adverse events and the recurrence rate after the procedure. Procedure-related adverse reactions were divided into intraprocedural bleeding, delayed bleeding, perforation, and postpolypectomy syndrome (abdominal pain, fever, leukocytosis, and peritoneal inflammation in the absence of frank perforation that occurs after colonoscopic polypectomy with electrocoagulation).[9] Intraprocedural bleeding was defined as requiring endoscopy therapy after ineffective lavage and snare-tip soft coagulation during colonoscopy, and delayed bleeding was defined as requiring blood transfusion and/or the need for surgery, an interventional radiology procedure or repeat colonoscopy within 30 days. Perforation was defined as requiring intervention, including endoscopic closure or surgery.

The quality of the included studies was assessed by two reviewers (YZ and HL) using the modified Newcastle-Ottawa scale (NOS) for case control and cohort studies, which ranges from 0 (low quality) to 5 (high quality). The representativeness of the cohort, assignment of exposure, outcome that was not present at the start of the study, assignment of outcome and adequate follow-up were evaluated for each study.

Statistical analysis

For each outcome, the effect of interest was measured by pooled proportions (%) with 95% confidence intervals (CIs), and heterogeneity among studies was assessed using Cochran's Q with the I^2 statistic. The pooled proportions were converted depending on the dependent variables modelled on the logit scale (R0 resection rate and en bloc resection rate) or double-arcsine scale (adverse event rate) and were pooled by a random effects model for a more conservative estimate if substantial heterogeneity (defined as I^2 statistic >50% and $P < 0.10$) was observed; otherwise, a fixed effect model was used. We also calculated the adverse event rate and recurrence rate in the form of frequencies over the total number of included patients. In addition, meta-regression analysis of properties, including temporal-spatial properties, such as country of study, and methodology-related properties, such as study sample size and endoscopic techniques, was performed on the main outcomes, and prespecified subgroup analysis was carried out according to variables that may have affected the results, such as hot or cold resection.

All meta-analytic computations were completed using R (version 3.6.2) and RStudio (RStudio Desktop version 1.1.463) statistical software with the meta and metafor packages.

RESULTS

Study characteristics and quality

Overall, 2397 articles were retrieved, and 36 studies were included in the final analysis [details in Figure 1], comprising data on 3212 polyps in total. Of the 36 studies [Table 1 and supplementary Table 2], 17 were retrospective, and the others were prospective. The number of studies of different origins were as follows: 9, United States; 8, Japan; 3, Australia; 3, China; 3, Greece; 2, Italy; and 1 each of Austria, Belgium, Brazil, Germany, Korea, Portugal, Spain and Sweden.

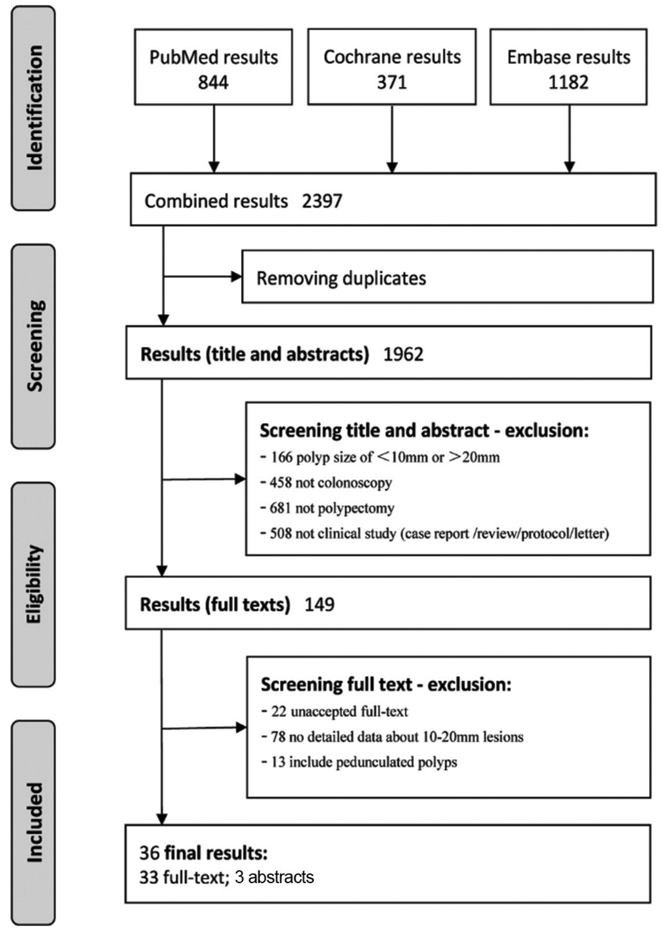

Figure 1: Flowchart of the study selection process

The quality scores assessed by modified NOS ranged from 4 to 5 (with a score of 4 accounting for 40.74% of studies, and a score of 5 accounting for 59.26%), excluding nine random controlled studies [Supplementary Table 3]. The heterogeneity was noted to be moderate–strong for the primary outcomes, as the majority of the studies were of one single group.

Different resection methods

Among the 36 articles with analysable data that we included, regardless of the type of resection method, 17 studies provided information on the R0 resection rate (representing 1201 lesions), and 28 studies provided information on the en bloc resection rate (representing 1391 lesions) [Figures 2 and 3]. The results

Table 1: Study characteristics

Author, year	Country	Lesions, *n*	Size and type of lesions*	Resection technique(s)	Quality**
Retrospective study					
Yokota T,[10] 1994	Japan	40	11-20-mm nonpedunculated†	EMR (NS+E)	4
Su MY,[13] 2005	China	58	11-20-mm nonpolypoid††	EMR (NS)	5
Huang Y,[17] 2009	China	30	10-19-mm LST	EMR (NS)	5
Serrano M,[18] 2012	Portugal	112	10-20-mm flat and sessile	EMR (NS/G+E+indigo)	5
Choksi N,[33] 2015	USA	8	10-20-mm adenoma	Cold EMR (NS+E+methylene blue)	5
Kashani A,[20] 2015***	USA	22	10-20-mm nonpedunculated	Cap-EMR	4
Muniraj T,[34] 2015	USA	15	10-20-mm sessile	Cold EMR (NS+indigo)	5
Hirose R,[39] 2017	Japan	72	10-14-mm nonpolypoid	CSP	5
Piraka C,[35] 2017	USA	35	10-20-mm nonpedunculated	Cap-cold EMR (NS+E+indigo)	5
Schenck RJ,[23] 2017	USA	34	15-20-mm nonpedunculated	EMR (NS) vs cap-UEMR	5
Cadoni S,[24] 2018	Italy	121	10-19-mm flat and sessile	EMR vs UEMR	5
Chien HC,[26] 2019	China	148	10-19-mm nonpedunculated	EMR vs UEMR	4
Gessl I,[40] 2019	Austria	432	11-20-mm sessile	CSP vs HSP	4
Kumar V,[27] 2019	USA	150	11-19-mm flat and sessile	EMR	5
Murakami T,[41] 2019	Japan	74	10-14-mm SSA/P	CSP	5
Van Overbeke L,[43] 2019	Belgium	63	11-19-mm flat and sessile	CSP/cold EMR	5
Ket SN,[44] 2020	Australia	604	10-20-mm flat and sessile	HSP/EMR vs CSP/cold EMR	4
Prospective study					
Yoshikane H,[11] 1999	Japan	7	10-20-mm LST	Cap-EMR (NS+E)	5
Bergmann U,[12] 2003	Germany	32	11-20-mm flat and sessile	Cap-EMR (NS+E)	5
Uraoka T,[14] 2005	Japan	140	10-19-mm LST	EMR (NS+G+fructose) vs EMR (NS)	5
Katsinelos P,[15] 2006	Greece	11	10-19-mm LST	EMR (D_{50}+E)	5
Katsinelos P,[16] 2008	Greece	40	10-19-mm sessile	EMR (D_{50}+E) vs EMR (NS+E)	RCT
Yoshida N,[19] 2012	Japan	46	11-20-mm nonpedunculated	EMR (0.13%HA+indigo) vs EMR (NS+indigo)	RCT
Pohl H,[42] 2013	USA	110	10-20-mm nonpedunculated	HSP	4
La Nauze R,[38] 2014***	Australia	129	10-20-mm sessile	CSP vs HSP	RCT
Uedo N,[30] 2015	Sweden	10	15-20-mm IIa	Cap-UEMR	4
Woodward T,[21] 2015	USA	11	16-20-mm flat and sessile	EMR (HPMC+NS+E+indigo)	RCT
Amato A,[31] 2016	Italy	14	10-20-mm flat and sessile	UEMR	4
Horiuchi A,[22] 2016	Japan	102	10-19-mm flat and sessile	Cap-EMR (NS+E) vs cap-HSP	RCT
Tutticci NJ,[36] 2017	Australia	89	10-20-mm SSA/P	Cap-cold EMR (4% G+methyleneblue+E)	5
Chaves DM,[32] 2018	Brazil	9	10-20-mm SSA/P	UEMR	4
Han SJ,[25] 2018	Korea	51	10-20-mm flat and sessile	EMR (NS+E) vs EMR (NS+E+indigo)	RCT
Papastergiou V,[37] 2019***	Greece	34	10-20-mm SSA/P	Cold EMR (methylene blue+NS)	4
Rodríguez-Sánchez J,[28] 2019	Spain	69	15-20-mm nonpedunculated	EMR (NS+indigo) vs UEMR	RCT
Yamashina T,[8] 2019	Japan	210	10-20-mm nonpedunculated	EMR (NS) vs UEMR	RCT
Yen AW,[29] 2020	USA	86	10-19-mm nonpedunculated	Cap-UEMR vs cap-EMR (HS+E+indigo)	RCT

CSP, cold snare polypectomy; D_{50}, 50% dextrose; E, epinephrine; EMR, endoscopic mucosal resection; G, glucose; HA, hyaluronic acid; HPMC, hydroxypropyl methylcellulose; HSP, hot snare polypectomy; LST, lateral spreading tumour; NS, normal saline; SSA/P, sessile serrated adenoma/polyp; UEMR, underwater endoscopic mucosal resection. *type of lesion according to the Paris classification. **quality evaluation using modified Newcastle-Ottawa scale. ***Only the abstract is available. †Nonpedunculated refers to all lesions except those classified as I_p. ††Nonpolypoid includes lesions of types II_a, II_b, and II_c

of the multivariate meta-regression analysis of the main outcomes are presented in Table 2. The effect of the variable of study design on the R0 resection rate was significant (prospective study vs retrospective study; $P = 0.03$), while the heterogeneity remained significant. Follow-up information was available for 329 lesions, and the median duration of follow-up was 15 months (range: 2–42). The pooled proportions of adverse events and recurrence were low, and the frequency rates are shown in Figure 4.

Endoscopic mucosal resection (EMR)

A total of 21 studies employed EMR, including eight studies with analysable data (381 lesions) on the R0 resection rate and 16 studies with analysable data (814 lesions) on the en bloc resection rate.[8,10-29] The pooled proportions for R0 resection rate and en bloc resection rate were 87% (95% CI 0.75–0.93, $I^2 = 83\%$) and 88% (95% CI 0.79–0.93, $I^2 = 89\%$), respectively.

The intraprocedural bleeding rate was 5.18% (19/367; pooled proportion 3%; 95% CI 0–0.08), ranking the highest among the intraprocedural bleeding rates of the conventional polypectomy methods. Other adverse events, such as delayed bleeding and postpolypectomy syndrome, had the lowest rates under EMR, but two perforations were reported. One was related to colonoscopy rather than EMR, and the other was caused by muscular involvement in snaring because of excessive suction.

Underwater endoscopic mucosal resection (UEMR)

Nine studies (of which only four provided eligible data on R0 resection rate and nine presented data on

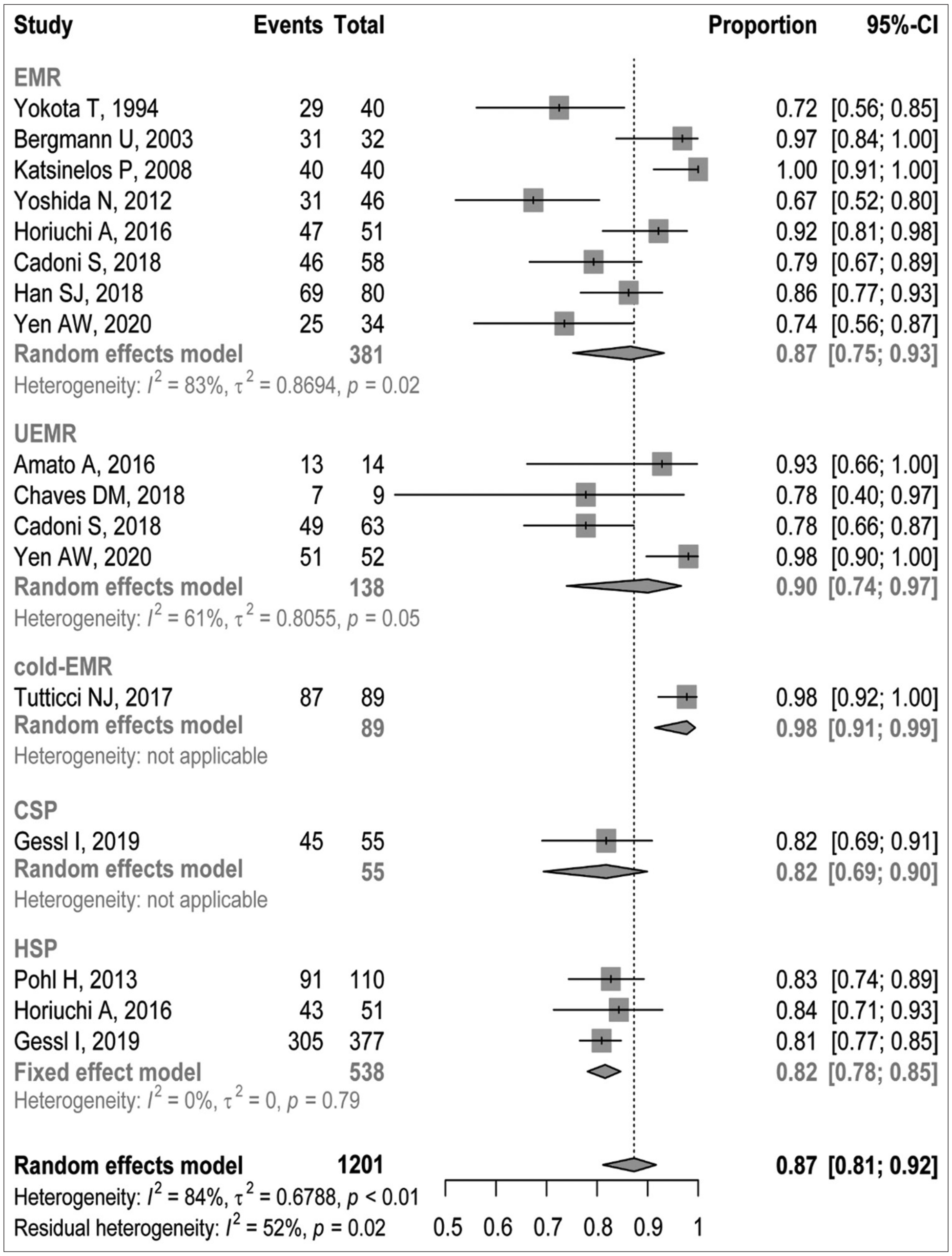

Figure 2: Forest plot reporting the R0 resection rates of different types of resection methods. (95% CI, 95% confidence interval; CSP, cold snare polypectomy; EMR, endoscopic mucosal resection; HSP, hot snare polypectomy; UEMR, underwater endoscopic mucosal resection)

en bloc resection rate) analysed the effectiveness of UEMR.[8,23,24,26,28-32] The pooled proportions were quite encouraging with this method (pooled proportion for R0 resection rate 90%, 95% CI 0.74–0.97, I^2 = 61%; pooled proportion for en bloc resection rate 82%, 95% CI 0.71–0.90, I^2 = 77%).

The rate of adverse events resembled that under EMR, with two cases of delayed bleeding reported in 271 lesions, although without a need for surgery. The recurrence rate (6.67%; 1/15) was only available from one study of 15 lesions.

Cold EMR

Five studies involving 181 lesions used cold EMR.[33-37] Only one of these studies provided analysable data (89 lesions) on the R0 resection rate, and among all of the resection rates, cold EMR yielded the highest pooled proportion (proportion 98%; 95% CI 0.91–0.99). There were no available data on the en bloc resection rate.

Only one in 124 lesions (0.81%) had intraprocedural bleeding, and one in 58 (1.72%) lesions had abdominal pain. No perforations were observed in 92 lesions.

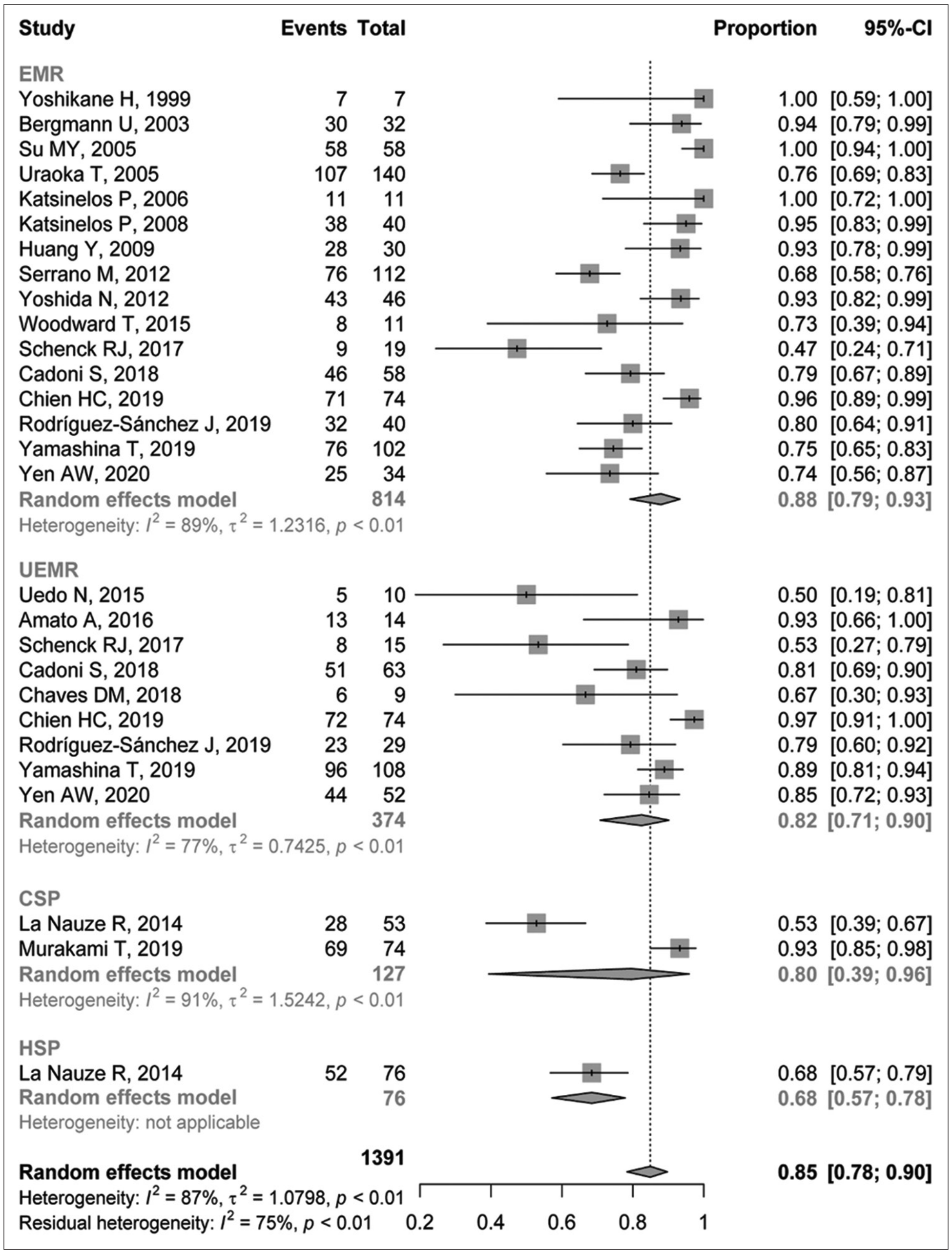

Figure 3: Forest plot reporting the en bloc resection rates of different types of resection methods. (95% CI, 95% confidence interval; CSP, cold snare polypectomy; EMR, endoscopic mucosal resection; HSP, hot snare polypectomy; UEMR, underwater endoscopic mucosal resection)

Cold snare polypectomy (CSP)

Only one eligible study (55 lesions) among the four studies (222 lesions) using CSP provided data on the R0 resection rate, but the pooled proportion was only 82% (95% CI 0.69–0.90).[38-41] The en bloc resection rate was reported in two studies involving 127 lesions, with values of 0.53 and 0.93, and the pooled proportion was 80% (95% CI 0.39–0.96, I^2 = 91%).

Seldom, no adverse events were noted, representing approximately 200 lesions. One patient using warfarin experienced delayed bleeding 4 days after CSP, but the bleeding was controlled with subsequent endoscopic clipping and did not require blood transfusion. Among the conventional polypectomy methods, CSP yielded the lowest recurrence rate, at 5.41% (4/74), according to the available data.

Hot snare polypectomy (HSP)

Four studies employed HSP: three with analysable data (538 lesions) on the R0 resection rate and one (76 lesions) with analysable data on the en bloc resection rate.[22,38,40,42] The R0 resection rate pooled proportion was 82% (95% CI 0.78–0.85, I^2 = 0%), similar to that under CSP, and among

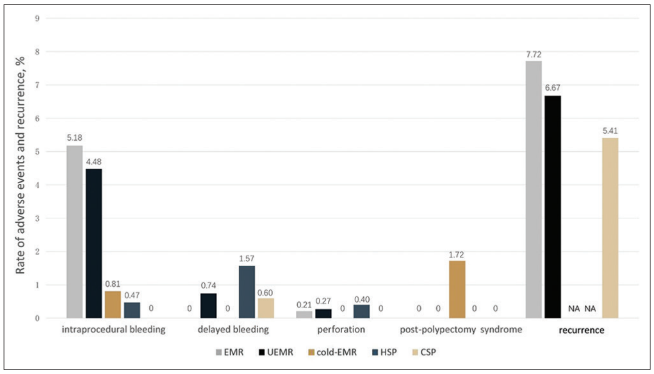

Figure 4: Bar diagram reporting outcomes for adverse events and recurrence. (CSP, cold snare polypectomy; EMR, endoscopic mucosal resection; HSP, hot snare polypectomy; UEMR, underwater endoscopic mucosal resection)

the methods, HSP was associated with the lowest en bloc resection rate (pooled proportion 68%; 95% CI 0.57–0.78).

The incidence rates of adverse events in HSP were 0.47% for intraprocedural bleeding (2/428; pooled proportion 0; 95% CI 0–0.01), 1.57% for delayed bleeding (2/127; pooled proportion 1%; 95% CI 0–0.05), and 0.4% for perforation (2/504; pooled proportion 0; 95% CI 0–0.01). No postpolypectomy syndrome was observed (0/127).

Subgroup analysis according to submucosal uplifting effect

Resection methods with a submucosal uplifting effect included EMR, UEMR and cold EMR. Thirteen studies (608 lesions) reported outcomes for the R0 resection rate, and 23 studies (978 lesions) reported data on the en bloc resection rate. The pooled proportions for complete and en bloc resection were 90% (95% CI 0.81–0.94, $I^2 = 84\%$) and 85% (95% CI 0.79–0.91, $I^2 = 83\%$), respectively.

For resection without a submucosal uplifting effect, four studies representing 593 lesions yielded a pooled R0 resection rate of 82% (95%CI 0.78–0.85, $I^2 = 0\%$); three studies involving 203 lesions yielded a pooled en bloc resection rate of 74% (95%CI 0.47–0.94, $I^2 = 94\%$).

The intraprocedural bleeding rate was slightly higher in the submucosal uplifting effect group (35/826; rate 4.24%; pooled proportion 3%; 95% CI 0.01–0.05, $I^2 = 43\%$) than in the no uplifting effect group (2/629; rate 0.3%; pooled proportion 0%; 95% CI 0–0.01, $I^2 = 0\%$). For delayed bleeding, perforation and postpolypectomy syndrome, the rates in both groups were low [Table 3a].

Subgroup analysis according to electrocautery usage (hot vs cold resection)

Removal methods using electrocautery were considered hot resection methods, such as HSP, EMR and UEMR. Based on the data reported for R0 resection rate by 17 studies (15 studies with 1057 hot resection-treated lesions and 2 studies with 144 cold resection-treated lesions), the pooled proportions were 86% (95% CI 0.80–0.91, $I^2 = 81\%$) and 93% (95% CI 0.72–0.99, $I^2 = 77\%$). For en bloc resection rate, the pooled proportions were 84% (95% CI 0.77–0.90) for hot resection and 65% (95% CI 0.26–0.91) for cold resection.[33-41,43,44]

Table 2: Multivariate meta-regression of primary outcomes according to temporal-spatial and methodological characteristics

Variable	R0 resection rate		en bloc resection rate	
	Coefficient	P	Coefficient	P
Time period of the study				
≤2015	Reference		Reference	
>2015	-0.07	0.43	-0.12	0.20
Origin of study				
Asia	Reference		Reference	
Western countries	0.12	0.10	-0.16	0.15
Study design				
Prospective	Reference		Reference	
Retrospective	-0.17	0.03†	0.0022	0.98
Sample size				
<50	Reference		Reference	
≥50	0.13	0.18	0.01	0.90
Resection with uplifting effect				
No	Reference		Reference	
Yes	0.11	0.21	0.26	0.17
Resection with electrocautery				
No	Reference		Reference	
Yes	-0.08	0.44	0.06	0.78

Positive meta-regression coefficients express an increased rate compared with the reference group. †statistically significant

The pooled proportions of adverse events for both groups were similar. However, intraprocedural bleeding was more frequent in the hot resection group, at 3% (95% CI 0.01–0.05, $I^2 = 68\%$), than in the cold resection group (pooled proportion 0%; 95% CI 0–0.01, $I^2 = 0\%$), whereas delayed bleeding exhibited the opposite pattern (pooled proportion for hot resection group 0%, 95% CI 0.01–0.03, $I^2 = 6\%$; pooled proportion for cold resection group 4%; 95% CI 0–0.07, $I^2 = 54\%$) [Table 3b].

DISCUSSION

The purpose of this systematic review was to summarize the available evidence and recommend the best method to remove 10- to 20-mm nonpedunculated colorectal polyps. Analysis of all the existing data showed that the resection methods with a submucosal uplifting effect (EMR, UEMR, cold-EMR), especially cold EMR, were safe and more effective than the methods without such an effect for removing 10- to 20-mm nonpedunculated colorectal polyps.

Table 3: Subgroup analysis outcomes

Outcome	With submucosal uplifting effect		Without submucosal uplifting effect	
	n	%	*n*	%
R0 resection rate	608	90% (95% CI, 0.81-0.94; I^2=84%)	593	82% (95% CI, 0.79-0.85; I^2=0%)†
En bloc resection rate	978	85% (95% CI, 0.79-0.91; I^2=83%)	203	74% (95% CI, 0.47-0.94; I^2=94%)†
Intraprocedural bleeding	826	3% (95% CI, 0.01-0.05; I^2=43%)	629	0% (95% CI, 0-0.01; I^2=0%)
Delayed bleeding	696	0% (95% CI, 0-0.01; I^2=0%)	241	1% (95% CI, 0-0.02; I^2=7%)†
Perforation	1380	0% (95% CI, 0-0.01; I^2=2%)	726	0% (95% CI, 0-0; I^2=0%)
Postpolypectomy syndrome	601	0% (95% CI, 0-0; I^2=0%)	180	1% (95% CI, 0-0.03; I^2=9%)†

(a) Pooled proportions according to presence of submucosal uplifting effect, CI, confidence interval. †Fewer than five studies were included in the analysis.

Outcome	Cold resection		Hot resection	
	n	%	*n*	%
R0 resection rate	144	93% (95% CI, 0.72-0.99; I^2=77%)†	1057	86% (95% CI, 0.80-0.91; I^2=81%)
En bloc resection rate	473	65% (95% CI, 0.26-0.91; I^2=97%)†	1522	84% (95% CI, 0.77-0.90; I^2=90%)
Intraprocedural bleeding	566	0% (95% CI, 0-0.01; I^2=0%)	1337	3% (95% CI, 0.01-0.05; I^2=68%)
Delayed bleeding	668	0% (95% CI, 0-0.03; I^2=6%)	938	4% (95% CI, 0-0.07; I^2=54%)
Perforation	618	0% (95% CI, 0-0; I^2=0%)	2023	0% (95% CI, 0-0; I^2=5%)
Post-polypectomy syndrome	415	0% (95% CI, 0-0; I^2=7%)	836	0% (95% CI, 0-0.02; I^2=59%)

(b) Pooled proportions according to electrocautery (cold vs hot resection), CI, confidence interval. †Fewer than five studies were included in the analysis.

When resecting lesions of this size, endoscopists often encounter two major challenges: one is determining whether submucosal uplifting or injection is needed, and the other in deciding between cold and hot resection. At present, EMR is the preferred method of resection in clinical practice.[45] This method takes advantage of the thermal effect of electricity to produce local hyperthermia, local tissue cell water liquefaction and protein coagulation denaturation after submucosal injection. With this method, a high-frequency current is used to produce hyperthermia of the tissues that come into contact with the snare; the polyp is then cauterized and cut off. Another new technology, UEMR, is similar in principle to EMR but does not involve submucosal injection.[46] Since it was first proposed by Binmoeller *et al.*[46] in 2012, many studies of UEMR have been conducted. Yamashina *et al.*[8] recently compared the effectiveness and safety of UEMR and EMR in the resection of intermediate-size colorectal polyps with encouraging results, suggesting that UEMR is a technique worth popularizing. It requires local insufflation with water instead of air in the bowel lumen, and the optical zoom effect can magnify the mucosal structure and indirectly enhance the sensitivity of the examination. In addition, surgery with water perfusion can alleviate pain in patients.

In the subgroup analysis according to submucosal uplifting effect, we found that the R0 resection rate and en bloc resection rate were better in the submucosal uplifting group (R0 resection rate 90% vs 82%; en bloc resection rate 85% vs 74%). A retrospective study of 10- to 20-mm neoplastic polyp resection with follow-up for 0.5 to 5 years found that incomplete resection, especially a high proportion of piecemeal resections, may be a risk for recurrence and interval CRC.[47,48] We believe that the submucosal uplifting effect can allow these flatter lesions to be more easily exposed, thus facilitating complete and en bloc resection. Although UEMR is not injected directly into the submucosal layer, the mucosa and submucosa float due to water immersion, while the muscularis external layer remains circumferential such that the two layers are separated from each other, which produces submucosal uplift.[46]

However, the analysis of adverse events showed that there was a larger proportion of adverse rates among the methods involving a submucosal uplifting effect. The incidence rates of intraprocedural bleeding were higher for EMR and UEMR (for EMR, 5.18%; 19/367; pooled proportion 3%; 95% CI 0–0.08; for UEMR, 4.48%; 15/335; pooled proportion 3%; 95% CI 0.01–0.06) than for the other methods. Intraprocedural bleeding leads to the extension of operation time and complicates postoperative management. Considering that this phenomenon may be caused by electrocautery, we conducted a subgroup analysis by electrocautery, i.e. cold vs hot resection. The results revealed that thermal resection was associated with a higher intraprocedural bleeding rate than cold resection, which confirmed our conjecture. Cold resection is generally believed to be typically associated with more intraprocedural bleeding; however, we found that the intraprocedural bleeding rate of hot resection was higher than that of cold resection. Chandrasekar *et al.*[49] reported similar intraprocedural bleeding rates (2% for hot EMR but 0.7% for cold EMR). We found that technical proficiency may be one of the influencing factors. The operators in the study by Cadoni *et al.* came from a community hospital, and the study did not mention EMR operation experience.[19] The operator in Chien's study had only about 200 cases of EMR resection experience.[20] The rate of intraprocedural bleeding was significantly higher in these two studies than in the other studies. Therefore, improving the operation skills of doctors may improve the safety of the operation.[50] Takayanagi *et al.*[51] studied the histology of cold and hot snare resection and demonstrated that hot snare resection may cause deeper damage than cold snare resection and often reaches the muscularis propria. Owing to the electrocautery damage to the larger and greater number of blood vessels in the deep layer of the submucosa, it is believed that hot resection is more likely than cold resection to cause bleeding and even perforation after the procedure.[51] Nevertheless, in analysing the available data, we found that these postpolypectomy adverse events were rare. Among the studies employing hot resection methods, only two cases of delayed bleeding after HSP, two cases of delayed bleeding after UEMR, and one case of delayed perforation after EMR were reported after different durations of follow-up of nearly 2000 cases of lesions.[18,23,24,38] We suspect that the liquid cushion under the mucosa or the broader distance from the muscularis propria may play a buffering role [Figure 5].

Since cold resection was introduced to remove medium-size sessile polyps in 25 cases in 1989, mechanical resection without electrocautery has been advocated and has attracted increasing interest from endoscopists in recent years due to its fewer complications.[52] In addition, the cauterization of lesions leading to poor-quality resected specimens will eventually result in inaccurate histopathological evaluations and mistakes in postoperative treatment and follow-up. In contrast, cold resection ensures a complete specimen, including normal tissue at least 1–2 mm around the lesion.[53] The submucosal uplifting effect makes the resection of the bottom of the lesion more complete. All of these features are helpful for obtaining a higher R0 resection rate. In clinical practice, protrusions are commonly observed after cold polypectomy, which creates concern for residual polyps. Although research on residual tissue is not clear, a study by Tutticci *et al.*[54] in 2015 revealed that the protrusions were mainly composed of submucosa and muscularis mucosa and did not contain residual polyp tissue or large vascular structures.

The most obvious limitation of this review was the marked statistical heterogeneity in the majority of primary outcomes, which persisted after meta-regression analysis and subgroup analyses. This heterogeneity precluded the robustness of the results and represents a critical issue. Variations in clinical procedures (such as differences in endoscope type, snare type, current, type of submucosal injection solution, use of an assistant instrument and endoscopist experience) and lesion type (sessile, flat, nonpolypoid, lateral spreading tumour, adenoma, sessile serrated adenoma/polyp) among included studies are inevitable. In addition, variable definitions of the R0 resection rate may have contributed to the results, although only histological negativity was considered to define complete resection in this study. Second, the follow-up time to determine lesion recurrence varied among the studies, and available data were limited, which may reflect the fact that management is often not satisfied after lesion resection in real clinical practice. Finally, there were few studies on cold resection techniques, and comparative data for inclusion in this study were lacking. CSP is strongly recommended in existing guidelines for the removal of small polyps but not for that of large polyps, and many endoscopists consider cold resection to have a higher risk of bleeding during operation; therefore, it is rarely used in daily practice for 10- to 20-mm polyps.[6,45] However, many studies have indicated that cold snare resection may be an effective and safer technique than hot snare resection for >10-mm polyp resection[55,56]

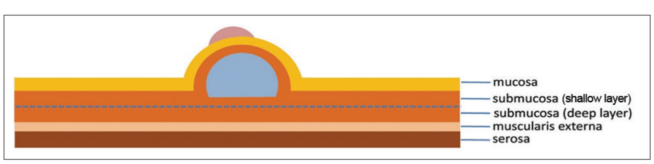

Figure 5: Schematic diagram of tissue after submucosal injection

CONCLUSIONS

Methods with submucosal uplifting effects seem to show better effectiveness than those without for the complete resection of 10- to 20-mm nonpedunculated polyps. In particular, cold EMR seems to be a promising method that exploits the advantages of cold resection; however, further research is needed.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: EMBASE search strategy

Query	Results
colonic: ab, ti OR colon: ab, ti OR colorectal: ab, ti	450782
polyp: ab, ti OR polyps: ab, ti OR lesion: ab, ti OR lesions: ab, ti OR neoplasia: ab, ti OR adenoma: ab, ti OR adenomas: ab, ti OR neoplasms: ab, ti	1369082
nonpedunculated: ab, ti OR 'nonpedunculated':ab, ti OR sessile: ab, ti OR nonpolypoid: ab, ti OR 'nonpolypoid':ab, ti OR excavated: ab, ti OR 'laterally spreading tumors':ab, ti OR 'laterally spreading lesions':ab, ti OR elevated: ab OR flat: ab, ti OR depressed: ab, ti	905822
#1 AND #2 AND #3	8484
polypectomy: ab, ti OR removal: ab, ti OR resection: ab, ti	821732
colonoscopy: ab, ti OR coloscopy: ab, ti	52020
#5 AND #6	9709
#4 AND #7 NOT review: it	1182

Supplementary Table 2: Original data of the included studies.

First author, year	R0 resection	En bloc resection	Intraprocedural bleeding	Delayed bleeding	Perforation	Post-polypectomy syndrome	Follow-up time	recurrence
EMR								
Yokota T, 1994	29	NA	NA	NA	NA	NA	NA	
Yoshikane H, 1999	NA	7	0	NA	1	NA	13.9±7.2 m	0/7
Bergmann U, 2003	31	30	NA	NA	NA	NA	18±6 m	0/30
Su MY, 2005	NA	58	NA	0	0	NA	22±8.5 m	0/58
Uraoka T, 2005	NA	107	NA	NA	0	NA	339±210 d	6/107
Katsinelos P, 2006	NA	11	NA	0	0	0	NA	
Katsinelos P, 2008	40	38	NA	NA	NA	NA	NA	
Huang Y, 2009	NA	28	NA	NA	0	0	NA	
Serrano M, 2012	NA	76	NA	NA	1	NA	15.9±8.9 m	12/74
Yoshida N, 2012	31	43	NA	NA	0	NA	NA	
Kashani A, 2015	NA	NA	1	NA	0	NA	NA	
Woodward T, 2015	NA	8	NA	NA	NA	NA	129±49.6 d	2/7
Horiuchi A, 2016	47	NA	0	0	0	0	NA	
Schenck RJ, 2017	NA	9	0	0	0	0	3-6 m	1/19
Cadoni S, 2018	46	46	9	0	0	0	14±12.96 m	NA
Han SJ, 2018	69	NA	NA	NA	NA	NA	NA	
Chien HC, 2019	NA	71	6	NA	0	NA	NA	
Kumar V, 2019	NA	NA	NA	NA	0	NA	NA	
Rodríguez-Sánchez J, 2019	NA	32	NA	NA	NA	NA	NA	
Yamashina T, 2019	NA	76	2	0	0	0	NA	
Yen AW, 2020	25	25	1	0	0	0	NA	
UEMR								
Uedo N, 2015	NA	5	NA	0	0	NA	NA	
Amato A, 2016	13	13	2	0	0	NA	NA	
Schenck RJ, 2017	NA	8	0	1	0	0	3-6 m	1/15
Cadoni S, 2018	49	51	5	1	0	0	14±12.96 m	NA
Chaves DM, 2018	7	6	0	0	0	NA	NA	
Chien HC, 2019	NA	72	3	NA	1	NA	NA	
Rodríguez-Sánchez J, 2019	NA	23	NA	NA	0	NA	NA	
Yamashina T, 2019	NA	96	3	0	0	0	NA	
Yen AW, 2020	51	44	2	0	0	0	NA	
Cold-EMR								
Choksi N, 2015	NA	NA	NA	0	0	1 (abdominal pain)	3 m	NA
Muniraj T, 2015	NA	NA	NA	0	0	0	NA	
Piraka C, 2017	NA	NA	0	0	0	0	NA	
Tutticci NJ, 2017	87	NA	1	NA	NA	NA	NA	
Papastergiou V, 2019	NA	NA	NA	0	0	0	NA	
CSP								
La Nauze R, 2014	NA	28	NA	0	0	0	NA	
Hirose R, 2017	NA	NA	0	1	0	NA	NA	
Gessl I, 2019	45	NA	0	NA	0	NA	NA	
Murakami T, 2019	NA	69	0	0	0	NA	10-24 m	4/74
HSP								
Pohl H, 2013	91	NA	NA	NA	NA	NA	NA	
La Nauze R, 2014	NA	52	NA	2	1	0	NA	
Horiuchi A, 2016	43	NA	0	0	0	0	NA	
Gessl I, 2019	305	NA	2	NA	1	NA	NA	

CSP, cold snare polypectomy; d, day; EMR, endoscopic mucosal resection; HSP, hot snare polypectomy; m, month; NA, not available; UEMR, underwater endoscopic mucosal resection

Supplementary Table 3: Modified Newcastle-Ottawa scale

First author, year	Selection			Outcome		Score
	1	2	3	1	2	
Yokota T, 1994	1	1	1	1	0	4
Yoshikane H, 1999	1	1	1	1	1	5
Bergmann U, 2003	1	1	1	1	1	5
Su MY, 2005	1	1	1	1	1	5
Uraoka T, 2005	1	1	1	1	1	5
Katsinelos P, 2006	1	1	1	1	1	5
Katsinelos P, 2008	-	-	-	-	-	RCT
Huang Y, 2009	1	1	1	1	1	5
Serrano M, 2012	1	1	1	1	1	5
Yoshida N, 2012	-	-	-	-	-	RCT
Pohl H, 2013	1	1	1	1	0	4
La Nauze R, 2014	-	-	-	-	-	RCT
Choksi N, 2015	1	1	1	1	1	5
Kashani A, 2015	1	1	1	1	0	4
Muniraj T, 2015	1	1	1	1	1	5
Uedo N, 2015	1	1	1	1	0	4
Woodward T, 2015	-	-	-	-	-	RCT
Amato A, 2016	1	1	1	1	0	4
Horiuchi A, 2016	-	-	-	-	-	RCT
Hirose R, 2017	1	1	1	1	0	4
Piraka C, 2017	1	1	1	1	1	5
Schenck RJ, 2017	1	1	1	1	1	5
Tutticci NJ, 2017	1	1	1	1	1	5
Cadoni S, 2018	1	1	1	1	1	5
Chaves DM, 2018	1	1	1	1	0	4
Han SJ, 2018	-	-	-	-	-	RCT
Chien HC, 2019	1	1	1	1	0	4
Gessl I, 2019	1	1	1	1	0	4
Kumar V, 2019	1	1	1	1	1	5
Murakami T, 2019	1	1	1	1	1	5
Papastergiou V, 2019	1	1	1	1	0	4
Rodríguez-Sánchez J, 2019	-	-	-	-	-	RCT
Van Overbeke L, 2019	1	1	1	1	1	5
Yamashina T, 2019	-	-	-	-	-	RCT
Ket SN, 2020	1	1	1	1	0	4
Yen AW, 2020	-	-	-	-	-	RCT

Selection variables: 1=representativeness of cohort; 2=assignment of exposure; 3=outcome not present at start. Outcome variables: 1=assignment of outcome; 2=adequate follow-up