Modified endoscopic mucosal resection techniques for treating precancerous colorectal lesions

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Abstract

Endoscopic mucosal resection (EMR) is a technique allowing efficacious and minimally invasive resection of precancerous lesions across the entire gastrointestinal tract. However, conventional EMR, involving injection of fluid into the submucosal space, is imperfect, given the high rate of recurrence of post-endoscopic resection adenoma, especially after piecemeal resection. In light of these observations, modifications of the technique have been proposed to overcome the weakness of conventional EMR. Some of them were designed to maximize the chance of *en bloc* resection—cap-assisted EMR, underwater EMR, tip-in EMR, precutting, assisted by ligation device—while others were designed to minimize the complications (cold EMR). In this review, we present their modes of action and summarize the evidence regarding their efficacy and safety.

Keywords Endoscopic mucosal resection, colorectal polyps, underwater, cold, cap

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Introduction

Colonoscopy with removal of adenomas reduces the incidence and mortality of colorectal cancer [1]. The vast majority of colorectal adenomas are diminutive (≤5 mm), posing no technical difficulty during removal [2]. Nonetheless, resection of larger (≥2 cm) adenomas, or those situated in difficult positions, e.g., between haustral folds, close to the dentate line or the ileocecal valve, can be challenging [3]. Endoscopic mucosal resection (EMR) is advocated as the first-line modality for removing large, flat or laterally spreading colorectal polyps [4]. Typically, the procedure starts with submucosal injection of a fluid underneath the lesion, aiming to create a submucosal cushion separating the lesion from the *muscularis propria*. This submucosal space expansion facilitates snaring of flat or sessile lesions, reduces the risk of transmural thermal injury and perforation, while it also indicates lesions where deeply invading neoplastic tissue is already present, preventing tissue lifting (the so-called "non-lifting sign") [5]. Still, it remains imperfect; the complete resection rate diminishes as polyp size increases, ranging from 2-30% when polyp size is greater than 10 mm [6], while more ominous is the high rate of recurrence of post-endoscopic resection adenoma, which may reach as high as 20%, especially with piecemeal EMR [7,8]. Moreover, submucosal injection can lead to significant operational difficulties, augmentation of lesion size and bleeding at the site of needle puncture [9,10]. On the other hand, evidence underlines that the procedure can be performed even without submucosal injection [11,12]. Aiming to address the aforementioned limitations and improve the procedure's outcomes, several modifications of the technique have been proposed [13]. This manuscript reviews the current literature, highlighting variations and modified EMR techniques used for colorectal lesions removal.

Materials and methods

We conducted a comprehensive review of the English literature published in the PubMed electronic database until October 2020. We used the following key words during our search: "endoscopic mucosal resection", "colorectal polyps", "underwater", "cold", "cap", "tip", band", and "outcome". All types of trials published in the English language were considered eligible for inclusion, while non-human, *ex-vivo* or pilot studies, editorials, narrative reviews, case reports/series, and video cases were excluded. For the purposes of this review, we present the evidence in a top-down approach, focusing mainly on the highest level, namely randomized controlled trials (RCTs) and meta-analyses, whenever possible. In the absence of the aforementioned categories of evidence, some of the strongest data available from other types of studies (i.e., cohort, cross-sectional, etc.) are discussed to underline the context of each technique.

Underwater EMR (U-EMR)

The technique

In U-EMR the lumen is filled with water, totally immersing the polyp without any fluid injection to the submucosal space, and resection follows using electrocautery current [14]. The initial observations that prompted the development of U-EMR arose during endosonography; there, it was noticed that water submersion preserves the circular shape of colonic *muscularis propria*, while the adenoma-bearing mucosa and submucosa layer may float away from the *muscularis propria* (Table 1) [5]. The presence of water also allows safe entrapment of the lesion within the snare, leaving out the *muscularis* layer, reducing the possibility of an immediate perforation (Fig. 1).

The evidence

Data from prospective and cohort studies

The first study to evaluate the efficacy and safety of this novel method was published in 2012 by Binmoeller *et al* [15]. The authors performed U-EMR for 62 colorectal lesions (>2 cm in size, mean size 34 mm) achieving 100% therapeutic efficacy and an excellent safety profile. These results were confirmed in subsequent prospective series and cohort studies [11,16-18]. Interestingly, in the study by Curcio *et al* [19], endoscopists with no previous specific dedicated training in U-EMR, achieved a 100% complete resection rate, signifying the method's "operator-friendly" character. So far, 6 RTCs have compared U-EMR and conventional EMR (C-EMR) in terms of polypectomy outcomes (i.e., *en bloc* and complete resection, adverse events rate and procedure time; Table 2) [20-25]. A large international study, recruiting 303 patients with 303 large (≥15 mm) colonic polyps, showed a significant benefit for U-EMR compared to C-EMR regarding curative resection, defined as presence of residual neoplasia on 3-6-month surveillance colonoscopy (8.5% vs. 16.8%, P=0.05). Moreover, a significantly higher rate of *en bloc* resection (48.1% vs. 24.1%, P<0.01) and a shorter resection total procedure time (10.8 vs. 13.2 min, P=0.01) were achieved by U-EMR [20]. Similar results were reported from a multicenter Japanese RCT [21]. The authors randomized patients with intermediate-sized (10-20 mm) sessile colorectal polyps to undergo either U-EMR or C-EMR, with R0 resection rate being the primary endpoint. Their analysis showed a significantly higher R0 resection rate when U-EMR was used: 69% (95%confidence interval [CI] 59-77%) vs. 50% (95%CI 40-60%), P=0.011. *En bloc* resection rate was also significantly higher: 89% (95%CI 81-94%) vs. 75% (95%CI 65-83%), P=0.007. Two more RCTs from Europe were published as abstracts [22,23]. The first [22] randomized 58 and 59 patients with large sessile or flat colonic lesions to U-EMR or C-EMR, respectively. Preliminary results of this study showed similar *en bloc* resection rates (27.6% for U-EMR vs. 18.6% for C-EMR, P=0.27) and adverse events rates (15.5% for U-EMR vs. 16.9% C-EMR, P=0.1). The second [23], a multicenter study, randomized 267 consecutive lesions (mean size 32.75 mm) to either U-EMR (n=126 including 15 recurrences) or C-EMR (n=141, 16 recurrences). U-EMR was beneficial in terms of complete (90% vs. 82%; P=0.04), but not *en bloc* (25% vs. 20%; P=0.56) resection rate. At 3-6 months, recurrence was higher in the C-EMR group, but the difference did not reach significance. In the largest RCT [24], incomplete resection rates did not differ between the 2 groups (2% vs. 1.9%, respectively, for U-EMR and C-EMR; P=0.91). Notably, no polypectomy-associated adverse events were reported in either group. In a multicenter RCT analyzing small colorectal polyps (4-9 mm) [25], both complete (83.1%, 95%CI 75.6-90.6% vs. 87.3%, 95%CI 80.7-94.0%; P=0.478 for U-EMR and C-EMR, respectively) and *en bloc* resection rate (94.4%, 95%CI 89.8-99.0% vs. 91.5%, 95%CI 86.0-97.1%; P=0.512 for U-EMR and C-EMR, respectively) were similar between the 2 groups. Considered overall, these prospective studies suggest that U-EMR may offer better complete resection rates compared with C-EMR, while reducing the risk of recurrences, but there are no definitive data on the *en bloc* resection rates. In any case, *en bloc* resection rate is closely related to polyp size [4]. For lesions <10 mm, the data suggest that neither of the 2 methods appears superior. However, the respective percentage with C-EMR for intermediate-sized (10-20 mm) or intermediate-to-large (20-30 mm) lesions drops significantly. This may be a result of suboptimal injection technique: the lesion may

Table 1 Main characteristics of modified EMR techniques

Technique	Basic principle	Advantages	Disadvantages
Underwater EMR	Water immersion preserves circular shape of colonic *muscularis propria* and separates mucosa and submucosa from the *muscularis mucosae*, allowing snare entrapment of the lesion while protecting against perforation and transmural thermal injury	High *en bloc* resection rate Low recurrence rate Low complication rate Reduced procedure time Easy to learn and perform No additional equipment needed; low cost High quality data support its use	Limited visibility due to intestinal peristalsis and poor bowel preparation
Cold EMR	After submucosal injection, the lesion is elevated with a margin of surrounding normal mucosa; resection is commenced at one side of the lesion margin, including a margin (3-4 mm) of normal tissue. The diameter of each tissue fragment should be limited to <10 mm for each resection	Less clinically significant bleeding Lower cost No deep mural injury Resection at polyp detection; no return for EMR No prophylactic clip Easier assessment of the scar Advantageous in resection of sessile serrated polyps	No advantage of ablation in reducing residual tissue Greater number of resected fragments Piecemeal resection of polyps 10-20 mm increases surveillance burden Need for dedicated snare Limited data for efficacy in conventional adenomas resection
Cap-assisted EMR	Using a transparent plastic cap mounted on the tip of the endoscope, after submucosal injection and elevation, the lesion is snared and drawn inside the cap using suction. Application of electrocautery finally resects the lesion	Facilitates operative field visualization Beneficial for lesions located in difficult sites, e.g.,, ileocecal valve Suction of normal mucosa lowers recurrence possibility Suction and insufflation of air unaffected	Increased perforation risk Need for large submucosal injection volume that may interfere with view Limited data for its use
Tip in EMR	After submucosal injection, a mucosal incision using the tip of the snare is made on the oral side of the lesion; the tip of the snare is anchored into the mucosal incision site and the lesion is grasped, while the tip of the snare remains anchored	High *en bloc* resection rate Reduced procedure time Easy to learn	Limited data for its use
EMR precutting	Following the submucosal injection, a circumferential incision is performed with an ESD knife. Next, a snare is used to capture the lesion at the mucosal circumferential incision site and removes the polyp	High technical success rate High *en bloc* resection rate Low recurrence rate	Increased complication risk Technically demanding procedure Higher cost For experienced endoscopists
EMR with ligation device	A multi-band ligation device is used on the tip of a colonoscope. Submucosal solution is performed, while the lesion is aspirated into the ligation device. After deployment of an elastic band the lesion is captured within the snare and then resection is performed below the band	Useful for small rectal neuroendocrine tumors Equal complete resection rate to ESD for rectal NETs Shorter procedural duration Shorter hospital admission	No data for its use in other colorectal lesions Additional cost

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NET, neuroendocrine tumor

be difficult to grasp when the fluid has not been applied homogenously underneath, while excessive fluid injection or bleeding by the needle may lead to lesion concealment. Contrariwise, U-EMR can indeed be advantageous for polyps ≥20 mm, or even larger, as the water-induced contraction of mucosa and submucosa layers may prevent already large lesions from extending further, allowing them eventually to be captured by normally sized snares [15].

Data from meta-analyses

Three meta-analyses pooled data regarding the efficacy and safety of U-EMR as a standalone procedure [12,26,27] (Table 2). Although their primary outcomes differed, they shared common conclusions. Spadaccini *et al* investigated outcomes from 508 lesions removed with U-EMR [12]. The pooled rate of complete resection was 96.36% (95%CI 91.77-98.44%), with

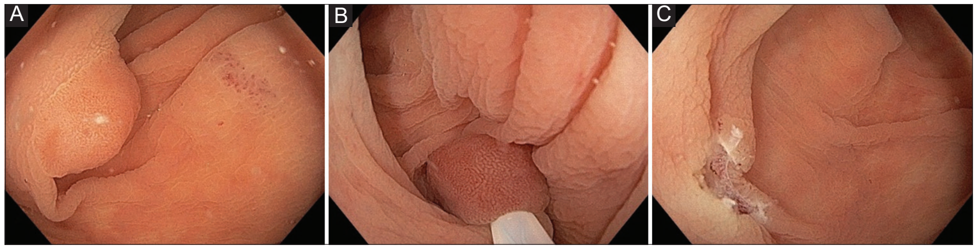

Figure 1 Example of a polyp resected by underwater endoscopic mucosal resection. (A) after air has been removed, the lumen is filled with water causing the polyp to float; (B) the polyp is captured *en bloc* within a snare; (C) final defect following *en bloc* underwater resection (Photos are from author's personal archive)

en bloc resection of 57.07% (95%CI 43.2-69.9%). Similarly, in another meta-analysis [26], the pooled *en bloc* resection rate was 59% (95%CI 43-75%; P<0.01), while the pooled rates for recurrence/residual adenoma and delayed bleeding were 5% (95%CI 2-8% and 2%, 95%CI 1-3%), respectively. The high degree of heterogeneity encountered (I^2=97%), calls for careful interpretation of these results. Finally, one recent meta-analysis evaluated the rate of adverse events and residual polyps, stratified by polyp size (10-19 mm and ≥20 mm) [27]. Pooled data for a total of 1142 polyps showed that adverse event and residual polyp rates were not significantly lower when U-EMR was applied for polyps of 10-19 mm (3.5% vs. 4.3% and 1.2% vs. 2.6%, respectively). The meta-regression analysis identified polyp size as an independent predictor for both complete (P=0.03) and *en bloc* resection (P=0.01).

Several meta-analyses compared U-EMR with conventional EMR (Table 2). A pooled analysis showed that U-EMR achieves higher *en bloc* resection rate (odds ratio [OR] 1.61, 95%CI 1.02-2.53; P=0.04) and lower rate of recurrence/residual adenoma (OR 0.18, 95%CI 0.07-0.46; P<0.01) [26]. Subsequently, 4 updated meta-analyses were published [28-31]. Kamal *et al* [28], demonstrated a significant benefit of U-EMR in terms of *en bloc* resection (risk ratio [RR] 1.16, 95%CI 1.08-1.26; P<0.001, complete resection rate confirmed by histology (RR 0.75, 95%CI 0.57-0.98; P=0.03), as well as local recurrence (RR 0.26, 95%CI 0.12-0.56; P<0.001). Choi *et al* assessed the outcomes from 614 polyps resected by U-EMR and 623 by C-EMR [29]. U-EMR resulted in higher rates of *en bloc* resection rate (OR 1.84, 95%CI 1.42-2.39; P<0.001). In another meta-analysis [30], U-EMR was associated with higher *en bloc* resection rate (85.87% vs. 73.89%; RR 1.14, 95%CI 1.01-1.30; P<0.05). Finally, in the most recent one [31], U-EMR was associated with a significantly lower rate of incomplete resection (OR 0.19, 95%CI 0.05-0.78; P=0.02) and recurrence (OR 0.41, 95%CI 0.24-0.72; P=0.002) compared to C-EMR. Moreover, the rates of both overall complications and intraprocedural bleeding were significantly lower with U-EMR (RR 0.66, 95%CI 0.48-0.90; P=0.008, and RR 0.59, 95%CI 0.41-0.84; P=0.004, respectively), underlining the safety of the procedure. Considered overall, these meta-analyses add new insights to the previously reported RCTs, suggesting that U-EMR achieves significantly higher *en bloc* resection rates and also confirming the lower recurrence rate associated with the technique compared to C-EMR.

Cold EMR

The technique

Electrical energy is pivotal for the efficacy and safety of polypectomy, allowing wider and deeper resection, reducing the possibility of residual neoplasia and expediting hemostasis [5]. On the other hand, the greater volume and depth of resected tissue may lead to thermal injury of the colonic wall and a higher risk of perforation [5]. Cold EMR is a hybrid technique (Table 1); submucosal injection and elevation of the lesion remain unaltered, but the resection is performed without the use of electrocautery (Fig. 2) [32]. However, the superiority of this procedure seems to diminish as the size of the polyp increases, suggesting a size-dependent efficacy [33,34].

The evidence

Data regarding the efficacy of cold EMR are limited, heterogeneous and of questionable quality (Table 3). Cold EMR performs well for non-pedunculated polyps sized 6-10 mm, achieving comparable rates of histological complete resection to C-EMR (92.8% vs. 96.37%) [35]. These results were corroborated by an RCT, where colorectal polyps 6-20 mm in size were randomly assigned to cold or C-EMR [36]. No differences in the core procedural outcomes were reported for cold EMR compared to C-EMR. Similarly, *en bloc* and histological complete resection by cold EMR were promising (cold EMR 82.5% vs. C-EMR 63.8%) [37]. Nonetheless, robust data assessing the performance in resection of larger polyps (≥20 mm) remain limited. In their study, Piraka *et al* [38] showed a residual or recurrent adenoma rate of 9.7%, with median polyp size being significantly larger in those with residual/recurrent adenoma (37.1 vs. 19.1 mm, P<0.001). The cardinal advantage of cold EMR is perhaps its excellent safety profile, with an extremely low rate of adverse events [39]. Intraprocedural bleeding may occur, usually in the form of minor oozing after resection; however, in most cases it lacks major clinical significance and can be easily managed [40,41]. Although sporadic cases have been reported [42], cold resection also bears zero risk for deep muscular layer injury, perforation or delayed bleeding [40]. Although data remain scarce, cold resection might be valuable for specific patient populations, such as those receiving anticoagulant/antiplatelet medication.

Table 2 RCTs and meta-analyses evaluating the effect of U-EMR on polypectomy outcomes

Randomized controlled trials comparing the effect of U-EMR vs. C-EMR on polypectomy outcomes

Author [Ref], year	Country	Study design	Study period	No. of centers	No. of endoscopists	No. of patients U-EMR vs. C-EMR	No. polyps U-EMR vs. C-EMR	Polyp size (mm) U-EMR vs. C-EMR	Complete resection rate (%) U-EMR vs. C-EMR	*En bloc* resection rate (%) U-EMR vs. C-EMR	Recurrent/residual Polyps (%) U-EMR vs. C-EMR	Total resection time* U-EMR vs. C-EMR	Adverse event rate (%) U-EMR vs. C-EMR
Hamerski *et al* [20], 2019, Abstract	United States, Italy	Multicenter, prospective randomized	10/2012 - 12/2017	4 (3 USA, 1 Italy)	NR	158 vs.145	158 vs.145	29 vs. 28.1	NR	48.1 vs. 24.1	8.5 vs. 16.8	10.8 min vs. 13.2 min	1.8 vs. 3.4
Yamashina *et al* [21], 2019	Japan	Multicenter, prospective randomized	02/2016 - 12/2017	5	28 (10 experts, 18 non-experts)	108 vs.102	108 vs. 102	14 vs. 13.5	† 69 vs. 50	†89 vs. 75	NR	175 (130-266) vs. 165 (117-274) s	2.8 vs. 1.9
Nagl *et al* [22], 2020, Abstract	Germany	Single-center prospective randomized	01/2019 - present	1	3	58 vs. 59	58 vs. 59	NR	NR	27.6 vs. 18.6	NR	12.5 min vs. 18.0 min	15.5 vs. 16.9
Rodríguez Sánchez *et al* [23], 2020, Abstract	Spain	Multicenter, prospective randomized	NR	14	NR	126 vs. 141	126 vs. 141	NR	† 90 vs. 82	25 vs. 20	9.1 vs. 17.6	20.7 min vs. 30.5 min	2.1 vs. 2.4
Yen *et al* [24], 2020	United States	Single-center prospective randomized	10/2016 09/2018	1	1	128 vs. 127	248 vs. 214	9.9 vs. 9.9	98 vs. 98.1	89.9 vs. 90.2	2 vs. 1.9	3.8 (0.34) vs. 5.4 (0.35), min	2 vs. 1.9
Zhang *et al* [25], 2020	China	Multicenter, prospective randomized non-inferiority	05/2019 11/2019	3	3	66 vs. 64	71 vs. 71	6.0 vs. 5.0	83.1 vs. 87.3	94.4 vs. 91.5	NR	72 (53-83) vs. 81 (52-113) s	1.4 vs. 1.4

(Contd...)

Table 2 *(Continued)*

Meta-analyses evaluating the efficacy and safety of U-EMR									
Author [Ref], year	Method	No. of studies included	Study design	No. of patients	Complete resection rate	*En bloc* resection rate	Recurrent/ residual polyp rate	Adverse event rate	Other outcomes
Spadaccini *et al* [12], 2018	U-EMR	10	7 prospective; 3 retrospective	433	Pooled rate: 96.36%, 95%CI (91.77-98.44)	Pooled rate: 57.07%, 95%CI 43.2-69.9	Pooled rate: 8.82%, 95%CI 5.78-13.25	Pooled rate: 3.31%, 95%CI 1.97-5.52	Lesion size (OR 1.21; 95%CI 1.07-1.37
Li *et al* [26], 2020	U-EMR	17	2 RCTs; 7 prospective; 8 retrospective	759	NR	Pooled estimate: 59%, 95%CI 43-75	Pooled estimate: 5%, 95%CI 2-8	Pooled estimate: 2%, 95%CI 1-3	NR
Li *et al* [27], 2020	U-EMR	18	2 RCTs; 10 prospective; 6 retrospective	1093	Pooled rate: 93.9%, 95%CI 91.0-96.8	Pooled rate: 58.7%, 95%CI 44.8-72.5	Pooled rate: 3.9%, 95%CI 1.2-6.7	Pooled rate: 3.6%, 95%CI 1.8-5.3	Mean polyp size independent factor for complete en bloc resection
Meta-analyses comparing the effect of U-EMR vs. C-EMR on polypectomy outcomes									
	Method vs. comparator	No. of studies included	Study design	No. of patients	Complete resection rate	*En bloc* resection rate	Recurrent/ residual polyp rate	Adverse event rate	Resection time
Li *et al* [26], 2020	U-EMR vs. C-EMR	17	2 RCTs; 7 prospective; 8 retrospective	759	OR 1.61, 95%CI 1.02-2.53	NR	OR 0.18, 95%CI 0.07-0.46	NR	NR
Kamal *et al* [28], 2020	U-EMR vs. C-EMR	7	2 RCTs; 1 prospective; 4 retrospective	1291	Pooled RR 1.28, 95%CI 1.18-1.39	Pooled RR 1.16, 95%CI 1.08-1.26	Pooled RR 0.26, 95%CI 0.12-0.56	Pooled RR: 0.68, 95%CI 0.44-1.05	NR
Choi *et al* [29], 2020	U-EMR vs. C-EMR	7	3 RCTs; 1 prospective; 3 retrospective	1313	NR	OR 1.84, 95%CI 1.42-2.39	OR 0.30, 95%CI 0.16-0.57	OR 1.11, 95%CI 0.57-2.17	MD: 5.42, 95%CI (-6.83 to -4.01)
Ni DQ *et al* [30], 2020	U-EMR vs. C-EMR	8	1 RCT; 1 prospective; 6 retrospective	1382	NR	RR 1.14, 95%CI 1.01-1.30	RR 0.27, 95%CI 0.09-0.83 at 3-6 months RR 0.43, 95%CI 0.20-0.92 at 12 months	RR 1.07, 95%CI 0.50-2.30	NR
Garg *et al* [31], 2020	U-EMR vs. C-EMR	9	3 RCTs; 1 prospective; 5 retrospective	1651	OR 2.20, 95%CI 1.26-3.83	NR	OR 0.41, 95%CI 0.24-0.72	RR 0.66, 95%CI 0.48-0.90	NR

*U-EMR, underwater endoscopic mucosal resection; C-EMR, conventional endoscopic mucosal resection; No., number; RCT, randomized controlled trial *: standard deviation or interquartile range; NR, not reported; OR, odds ratio; RR, risk ratio; RR, relative risk; MD, mean difference; CI, confidence interval*

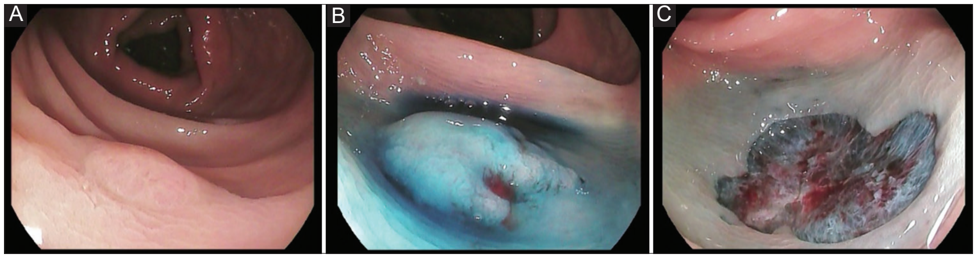

Figure 2 Example of a sessile serrated polyp resected by cold endoscopic mucosal resection (EMR). (A) 10-mm ascending colon sessile serrated polyp with indistinct borders; (B) submucosal injection with normal saline and indigo carmine solution without epinephrine; (C) final cold EMR defect (Photos are from author's personal archive)

Data from meta-analyses

The efficacy and safety for resecting non-pedunculated colorectal polyps >10 mm by cold EMR was the primary focus of a recent systematic review [40] (Table 3). The effect of the resection technique was evaluated via a subgroup analysis. Pooled analysis from 5 studies where cold EMR was performed for resection of polyps ≥10 mm, showed a complete resection rate of 99.1%, a residual polyp rate of 4.7% and an overall adverse event rate of 1.3% [40]. It should be also highlighted that all the adverse events referred to intraprocedural bleeding or post-polypectomy abdominal pain, while no case of perforation or postprocedural bleeding was recorded.

Cold EMR for sessile serrated polyps (SSPs)

The efficacy of cold EMR seems to depend on the histological type of the adenoma. The reasons behind this finding remain unknown and speculative, based on the different biological properties of each lesion and the suboptimal polypectomy technique. In an early retrospective study of 30 patients with SSPs of mean size 19 mm, an adenoma recurrence rate of 2.9% was noted [43]. Contrariwise, no recurrence was observed after resection of large (≥20 mm) SSPs in a prospective observational study [39]. Two retrospective studies focusing exclusively on SSPs reported high complete resection rates along with very low residual or recurrent polyp rates [44,45]. In one of the largest studies so far [46], cold EMR outcomes of 566 SSPs ≥10 mm, removed from 312 patients, were retrospectively assessed and a residual rate of 8% (5-12.1%) was reported. Van Hattem *et al* also examined cold versus C-EMR for the treatment of large (≥20 mm) SSPs [41], with similar recurrence rates, but cold EMR surpassed the conventional method with respect to safety, since it totally eradicated adverse events (delayed bleeding and perforation). Data from individual studies have been verified in a meta-analysis that evaluated the resection outcomes of SSPs sized 10 mm or larger [47]. Cold EMR was associated with a significantly lower residual polyp rate (0.9% vs. 5%; P=0.01) and less delayed bleeding (0% vs. 2.3%; P=0.03) compared to C-EMR. Taking these observations into account, cold EMR is perhaps the new treatment modality for large SSPs; however, its exact impact on the resection outcomes of conventional adenomas is ambiguous. Data from only 2 studies comparing the residual neoplasia rate from groups of conventional and serrated adenomas are at hand [38,43]; their results show higher residual neoplasia rates when cold EMR was applied for adenomas rather than SSPs.

Cap-assisted EMR

The technique

The cap is a single-use, transparent plastic device mounted on the distal end of the colonoscope. Beyond its undisputed usefulness in improving colonoscopy outcomes, this add-on device facilitates mucosectomy by maintaining sufficient distance between the scope tip and the lesion. During cap-assisted EMR, the polyp is initially lifted with submucosal fluid injection in a standard manner and the cap is placed against the polyp. The lesion is snared and retracted into the cap using gentle suction until an adequate amount of tissue has been captured; this is followed by total closure of the snare and resection by electrocautery [13]. The main advantage is associated with the optimal visualization of the resection field and suction of adequate normal mucosa. On the other hand, the technique entails a significant risk of perforation, given the potential entrapment of *muscularis propria* within the cap (Table 1).

The evidence

There are no randomized trials comparing the cap-assisted technique with C-EMR. The first evidence regarding safety came from a study [48] where analysis of 282 lesions (146 SSPs and 136 lateral spreading tumors) showed a complication rate of 8.6% and a local recurrence rate of only 4% (Supplementary Table 1). Favorable conclusions were also reached in a subsequent study [49] that reported eradication and complication rates of 91% and 10.2%, respectively. Intraprocedural or delayed bleeding occurred more frequently (3.9% and 2.4%, respectively) but were all successfully treated by endoscopic means, while among the perforation cases (n=5, 3.9%), only a minority (n=2) finally required surgical treatment. An interesting spin-off is the potential advantage of the cap in facilitating visualization and thus resection of lesions located in difficult colonic sites, e.g., the ileocecal valve (ICV) [50]. Indeed, cap-assisted EMR seems to offer the potential to overcome the objective difficulties

Table 3 Data from studies evaluating the efficacy and safety of cold EMR

Author, [Ref], year	Country	Study design	Study period	No. of centers	No. of endoscopists	No. of patients	No. polyps	Polyp size (mm)	Complete resection rate (%)	*En bloc* Resection rate (%)	Recurrent/ residual Polyps (%)	Resection time	Adverse event rate (%)
Trials evaluating the efficacy and safety of cold EMR													
Muniraj *et al* [43], 2015	United States	Single-center, retrospective	01/2012 10/2013	1	1	30	30	19	NR	6.4	20	57.37 (17.13) min	0
Tutticci *et al* [39], 2018	Australia	Single-center, prospective	NR	1	2	99	163	17.5	NR	NR	0.6	NR	0.3
Piraka *et al* [38], 2018	United States	Single-center, retrospective	10/2013 - 09/2015	1	1	73	94	20	NR	NR	9.7	53 min	0
Rameshshanker *et al* [44], 2018	United Kingdom	Single-center, retrospective	NR	1	NR	10	29	29.5	NR	0	0.1	NR	0
Yabuuchi *et al* [37], 2019	Japan	Single-center, prospective	03/2018 12/2018	1	5	72	80	12	63.8	82.5	NR	NR	0
Mangira *et al* [45], 2020	Australia	Multicenter, retrospective	01/2016 12/2017	5	5	186	204	25.5	NR	NR	5.5	NR	5.4
McWhinney *et al* [46], 2020	United States	Single-center, retrospective	02/2016 12/2019	1	1	312	566	17.2	NR	NR	8	NR	3.9
van Hattem WA *et al* [41], 2020	Australia	Single-center, retrospective	04/2016 01/2020	1	1	Cold vs. C-EMR 121 vs. 353	Cold vs. C-EMR 156 vs. 406	Cold vs. C-EMR 25 vs. 25	Cold vs. C-EMR 100 vs. 99	NR	Cold vs. C-EMR 4.3 vs. 4.6	Cold vs. C-EMR 10 vs. 10 min	Cold vs. C-EMR 0 vs. 5.1%
Randomized controlled trials comparing the effect of cold EMR vs. C-EMR on polypectomy outcomes													
Papastergiou *et al* [35], 2017¶	Greece	Dual-center, prospective randomized, noninferiority	01/2016 10/2016	2	2	77 vs.78	83 vs.81	8.2 vs.8.3	92.8 vs. 96.3	NR	NR	NR	3.6 vs. 1.2
Li *et al* [36], 2020¶¶	China	Single center, prospective randomized	07/2017 03/2019	1	5	132 vs.137	252 vs.267	12.0 vs.12.2	94.1 vs.95.5	95.3 vs.97.5	NR	3.27 vs.3.41	4.4 vs.1.9*

(Contd...)

Table 3 (Continued)

Meta-analysis evaluating the efficacy and safety of cold EMR

Author, [Ref], year	Method assessed	No. of studies included	Study design	No. of Patients	Complete resection rate	Recurrent/residual polyp rate	Adverse event rate
Thoguluva Chandrasekar *et al* [40], 2020*	Cold EMR	5	2 prospective; 3 retrospective	466	Pooled rate 99.1, 95%CI 98.0-100	Pooled rate 4.7, 95%CI 0.7-10.1	Pooled rate 1.0, 95%CI 0.00-0.025
Thoguluva Chandrasekar *et al* [47], 2020**	Cold EMR	2	1 prospective; 1 retrospective	911	NR	Pooled rate 0.9, 95%CI 0.5-1.9	Pooled rate 0.7, 95%CI 0.7-1.9

study comparing cold vs. C-EMR for non-pedunculated colorectal polyps sized 6-10 mm; ¶¶: study comparing cold vs. C-EMR for non-pedunculated colorectal polyps sized 6-20 mm; : this refers to the intraprocedural bleeding rate, immediately after polypectomy; delayed bleeding was higher in the C-EMR group than in the cold EMR group (2.6% vs. 0.8%; P=0.215); *pooled analysis evaluating resection of non-pedunculated colorectal polyps larger than 10 mm; **study evaluating only resection outcomes of sessile serrated polyps

EMR, endoscopic mucosal resection; C-EMR, conventional endoscopic mucosal resection; No., number; RCT, randomized controlled trial; NR, not reported; CI, confidence interval

of C-EMR in treating ICV polyps, even in the hands of less experienced endoscopists [51].

Tip-in EMR

The technique

Tip-in EMR, or anchored snare-tip EMR, is a simple modification of the conventional EMR procedure. After submucosal injection, a small mucosal incision is made on the oral side of the lesion. Subsequently, the tip of the snare is anchored into the mucosal incision site, allowing the lesion to be grasped entirely, while the tip of the snare remains anchored (Table 1).

The evidence

Despite its modest appearance, this modification has shown impressive preliminary results (Supplementary Table 1). In a retrospective case-control study, tip-in EMR achieved a significantly higher *en bloc* resection rate (n=39/43, 90.7% vs. n=58/83, 69.8%) and shorter treatment duration (6.64±0.64 vs. 10.47±0.81 min) compared to C-EMR, for resecting polyps with an average size of 22.9 mm and 24.3 mm, respectively. Recurrence and perforation rates were also similar between the 2 techniques (0% vs. 7.0% and 4.6% vs. 3.6%, respectively) [52]. Promising results were also obtained from a European multicenter study that evaluated the same method, but under the name "anchoring EMR" [53]. The authors managed to achieve a high proportion (82.8%) of R0 resection for lesions <20 mm in size, without any perforations. However, the method's efficacy decreased as the size of the lesion increased (50.0% >30 mm). Similarly, *en bloc* resection rates were reported to be 89.5% for 15-19 mm lesions and 76.2% for 20-25 mm lesions [54]. In another study [55], 46 sessile polyps or laterally spreading tumors with a mean size of 20.4 mm were removed. *En bloc* resection was feasible in all cases, while only one patient had local recurrence. Noh and colleagues reported that tip-in EMR is superior to C-EMR in terms of *en bloc* and complete histologic resection (94.7% vs. 77.0%, P=0.018, and 76.3% vs. 54.1%, P=0.022, respectively) [56].

EMR precutting

The technique

This technique is a mixture of C-EMR and endoscopic submucosal dissection (ESD), allowing endoscopists unfamiliar with ESD to resect large polyps *en bloc* [57]. The solution is injected into the submucosal layer underneath the lesion and a circumferential incision is performed with an ESD knife. Next, a snare is used to capture the lesion at the mucosal circumferential incision site and it is removed by applying the usual polypectomy technique (Table 1).

The evidence

In practical terms, this is the hybrid/simplified ESD, or knife-assisted EMR [13]. In an early study, outcomes from 523 non-pedunculated colorectal tumors (499 patients) treated with C-EMR, EMR precutting or ESD were reviewed [58] (Supplementary Table 1). EMR precutting achieved significantly higher *en bloc* (65.2% vs. 42.9%, P<0.001) and complete resection (59.4% vs. 22.9%, P<0.001) rates, and lower recurrence rates (3.1% vs. 25.7%, P<0.001), compared to C-EMR. Similarly, the method achieved a high *en bloc* resection rate when evaluated for the resection of large (mean size 25 mm) colorectal neoplasms [59]. EMR precutting was compared to ESD, conventional EMR and piecemeal EMR, in terms of complications and local recurrence rates, in another large study assessing colorectal laterally spreading tumors larger than 20 mm [60]. No cases of recurrence were reported in the EMR precutting group, a rate similar to ESD (0/27, 0% vs. 0/56, 0%) and lower than c-EMR (1/69, 1.4%). A variation of EMR precutting, under the term "knife-assisted snare resection" (KAR) has been evaluated in 2 studies from the same center [61,62]. The former [61] showed that the technique can perform well in difficult situations (scarred colonic polyps due to previous EMR attempt). The latter [62], analyzing outcomes from 170 colorectal polyps with a mean size of 46 mm, showed that KAR achieves adequate rates of *en bloc* resection (70/170, 41%), with low recurrence (21/160, 13.1%) and overall complication (14/170, 8.2%) rates. EMR precutting was compared to c-EMR in one study [63], where it achieved significantly higher *en bloc* and histological complete resection rates (88.6% vs. 48.5%, P<0.001, and 71.4% vs. 42.9%, P=0.02, respectively, for lesions ≥20 mm; 98.0% vs. 85.7%, P=0.004, and 87.8% vs. 67.3%, P<0.001, respectively, for <20 mm). A subsequent study went a step further, comparing EMR precutting to ESD [64]. EMR precutting was inferior to ESD regarding *en bloc* (61.5% vs. 96.6%; P=0.001) and complete resection rate (51.6% vs. 75.9%; P=0.009), but much safer. These results were replicated in a study that compared the outcomes of endoscopic resection for colorectal laterally spreading tumors [65]. ESD outperformed EMR precutting in terms of *en bloc* (87.4% vs. 51.3%, P<0.001) but not complete resection rate (90.3% vs. 92.3%, P=0.11); notably, the perforation rate was significantly higher for EMR precutting compared to ESD.

Data from meta-analyses

The efficacy and safety of the technique were evaluated in a recent systematic review and meta-analysis [66]. Analysis from 12 studies, including 720 colorectal lesions from Asian and non-Asian countries, showed that the hybrid technique achieved an overall pooled R0 resection rate of 60.6% (40.6-77.5) and an *en bloc* resection rate of 68.4% (51.7-81.3), with both outcomes being higher in Asian vs. non-Asian countries. Perhaps the most interesting finding to emerge was that only a single adverse event, out of 655 lesions from 10 studies analyzed, eventually needed surgical intervention, yielding a pooled rate for adverse events needing surgery post-procedure of 1% (95%CI 0.4-2.3%). The standard ESD technique was associated with significantly higher R0 (OR 2.44, 95%CI 1.23-4.85) and *en bloc* (OR 6.03, 95%CI 2.18-16.66) resection rates compared to EMR precutting. However, ESD remains a technically demanding procedure with a slow learning curve, particularly in western countries [67]. In this regard, EMR precutting could be a useful alternative for less experienced endoscopists or those in the first levels of the learning curve.

EMR with band ligation (EMR-L) or endoscopic submucosal resection with ligation (ESMR-L)

The technique

The band and snare procedure involves the use of a multi-band ligation device placed at the distal end of the scope. Submucosal injection in this technique is not always necessary and tissue is aspirated into the ligation device, followed by deployment of an elastic band [68]. The tissue is resected below the band using electrical current and clips are placed at the resection site in order to avoid complications. The main advantage is that it allows a deeper resection plane. It has been proven particularly effective for resection of lesions that extend to the submucosal layer, e.g., neuroendocrine tumors (NETs) [69].

The evidence

The initial evidence supporting the efficacy and safety of this method was published in 2003 [70]. ESMR-L was used for resecting 14 rectal carcinoid tumors (mean size 7.3 mm), achieving 100% therapeutic efficacy compared to conventional polypectomy (histopathologically proven negative margins: 0/14, 0% vs. 6/14, 43%, P<0.05, respectively), along with a zero complications rate (Supplementary Table 1). Notably, these favorable results were also replicated within larger series of patients that followed [71]. In a dual-center retrospective study, ESMR-L yielded a significantly higher R0 resection compared to C-EMR (17/19, 89.5% vs. 7/14, 50.0%, P<0.05) for removal of rectal carcinoid tumors with size ≤10 mm [72]. Similar conclusions were reached by a prospective, multicenter trial where ESMR-L not only achieved a significantly higher complete resection rate compared to C-EMR (42/45, 93.3% vs. 36/55, 65.5%, P=0.001) for same-size tumors, but also an equivalent complication rate (2/45, 4.4% vs. 0/55, 0.0%, P=0.2) [73]. In another study, ESMR-L once again outperformed C-EMR in terms of histologically complete resection (27/29, 93.1% vs. 82/110, 74.5%, P=0.03) for rectal neuroendocrine tumors with average size 7 mm, while at the same time the technique also showed valuable results in the long term [74,75]. Preliminary data suggested that the method even achieves at least equal resection outcomes to ESD for rectal carcinoid tumors <10 mm in size (complete resection rate 24/29, 82.8% vs. 25/31, 80.6% P=0.83) [76]; however, more recently it was shown that ESMR-L may in fact be even more superior to ESD for similar lesions, with respect to therapeutic outcomes and procedure time (95.5% vs.75.0%, P=0.02 for complete resection rate and 7.1±4.5 vs. 24.2±12.1 min, P<0.001, for resection time, respectively) [77]. In the largest prospective study comparing the efficacy and safety of the method and ESD for small rectal NETs (≤10 mm) [78], ESMR-L outperformed ESD, achieving a significantly higher pathological complete resection rate (53/53, 100% vs. 13/24, 54.2%, P<0.001). In one meta-analysis [79], the authors showed that the method achieves a higher complete resection rate than ESD (OR 4.08, 95%CI 2.42-6.88; P<0.001). These data suggest that this method may be considered the first-line option for treating small rectal NETs (≤10 mm).

Critical appraisal and conclusions

Addition of water prior to mucosectomy is the modification most widely reported in the literature. It has been validated in RCTs and meta-analyses, concerning all aspects of the procedure. Still, one should have in mind that the abovementioned studies were conducted in tertiary referral centers by expert endoscopists; thus, the generalizability of their results is questionable. Cold EMR is the "new kid on the block", as it puts an end to the use of electric current. Its impact on procedure safety is appealing; however, there are still unresolved issues, namely the efficacy when resecting larger conventional adenomas. Tip-in EMR is a promising technique given its simplicity, but further trials are definitely necessary before firm conclusions regarding its effectiveness can be reached. The issue of safety practically restricts the use of cap-assisted EMR to expert hands, while EMR precutting is perhaps valuable only as an intermediate step to achieve competence in ESD. Finally, EMR-L can be a rewarding, handy option, but its efficacy has been tested only for rectal lesions. Despite appearing beneficial in terms of improving EMR outcomes, concerns about the quality of the studies are raised. Most of them were conducted by expert endoscopists across tertiary centers, limiting the generalizability of the results to other real-world clinical practice settings. In addition, the majority were single-center and of retrospective design, enrolling populations with different baseline lesion characteristics and evaluating inconsistent endpoints, or simply aiming to provide results regarding the feasibility of a method rather than comparative evaluations of different approaches. It is imperative for future studies to enroll larger cohorts that will not only broaden the evidence for efficacy, but will enable them to detect changes in clinical and procedural outcomes.

Concluding remarks

Modifications of the basal technique enhance EMR performance when treating colorectal adenomatous lesions. Each method bears distinct advantages, but also suffers from considerable caveats. Evidence to support their large-scale use may be lacking at this time, but endoscopists should be aware of these techniques and might consider adopting one of these innovative treatment modalities on a case-by-case basis.

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Supplementary Table 1 Data from studies evaluating the efficacy and safety of other EMR modifications (cap-assisted EMR, tip-in EMR, EMR precutting, EMR band ligation)

Studies evaluating the efficacy and safety of cap-assisted EMR

Author [Ref], year	Country	Study design	Study period	No. of centers	No. of endoscopists	No. of patients	No. polyps	Polyp size (mm)	Complete resection rate (%)	*En bloc* resection rate (%)	Recurrent/ residual polyps (%)	Total resection time*	Adverse event rate (%)
Conio *et al* [48], 2010	Italy	Dual-center, prospective	01/2000 12/2007	2	NR	255	282 (146 SSPs, 135 LSTs)	25 for SSPs, 30 for LSTs	NR	0.0	4.0	40 min	8.6
Kashani *et al* [49], 2016	United States	Single-center, retrospective	06/2009 10/2013	1	1	97	124	NR	91.0	NR	NR	NR	10.2
Conio *et al* [50], 2010	Italy	Dual-center, Case series	01/2006 07/2008	1	NR	7	7	40	NR	NR	0.0	50min	28.5
Lew *et al* [51], 2019	United States	Single-center, retrospective	07/2008 11/2018	1	1	21	21	15	100.0	33.3	33.3	NR	24.0

Studies evaluating the efficacy and safety of Tip-in EMR

Author [Ref], year	Country	Study design	Study period	No. of centers	No. of endoscopists	No. of patients	No. polyps	Polyp size (mm)	Complete resection rate (%)	*En bloc* resection rate (%)	Recurrent/ residual polyps (%)	Total resection time*	Adverse event rate (%)
Pioche *et al* [53], 2019	France	Multi-center, retrospective	05/2017 01/2018	4	10	125	141	19.8	70.2	84.6	NR	NR	4.0
Imai *et al* [54], 2020	Japan	Single-center, retrospective	03/2014 12/2016	1	NR	72	78	NR	NR	85.9	0.0	NR	1.3
Lee *et al* [55], 2019	Taiwan	Single-center, retrospective	09/2015 09/2017	1	1	42	46	20.4	NR	100.0	5.0	14.9 min	2.2
Sato *et al* [52], 2020¶	Japan	Single-center, retrospective	01/2010 01/2019	1	6	Tip-in vs. C-EMR 43 vs. 83	Tip-in vs. C-EMR 43 vs. 83	Tip-in vs. C-EMR 22.9 vs. 24.3	Tip-in vs. C-EMR 76.3 vs. 54.1	Tip-in vs. C-EMR 90.7 vs. 69.8	Tip-in vs. C-EMR 0.0 vs. 7.0	Tip-in vs. C-EMR 6.64 min vs. 10.4 min	Tip-in vs. C-EMR 46 vs. 3.6
Noh *et al* [56], 2020¶	Korea	Single-center, retrospective	01/2018 09/2018	1	1	Tip-in vs. C-EMR 27 vs. 53	Tip-in vs. C-EMR 38 vs. 74	Tip-in vs. C-EMR 13.2 vs. 13.2	Tip-in vs. C-EMR 76.3 vs. 54.1	Tip-in vs. C-EMR 94.7 vs. 77	NR	Tip-in vs. C-EMR 178 sec vs. 149 sec	Tip-in vs. C-EMR 11.1 vs. 0.0

(Contd...)

Supplementary Table 1 *(Continued)*

Studies evaluating the efficacy and safety of EMR precutting

Lee *et al* [58], 2012	Korea	Single-center, retrospective	01/2004 11/2009	1	3	69	699	28.9	59.4	65.2	3.1	NR	15.9
Sakamoto *et al* [59], 2012	Japan	Single-center, retrospective	03/2008 07/2009	1	2	24	24	20.9	NR	67.0	0.0	40.0	0.0
Terasaki *et al* [60] 2012	Korea	Single-center, retrospective	04/2006 12/2009	1	2	28	28	20.9	NR	NR	0.0	NR	NR
Chedgy *et al* [61] 2012	UK	Single-center, prospective	2007 2014	1	NR	37	37	40.0	NR	38.0	16.0	NR	8.0
Bhattacharyya *et al* [62], 2012	UK	Single-center, prospective	2007 2013	1	1	170	348	46.0	NR	41.0	13.1	150	8.2
Yoshida *et al* [63], 2019¶¶	Japan	Multicenter, retrospective	04/2011 05/2018	3	NR	EMR precutting P vs. C-EMR 98 vs. 98	EMR precutting vs. C-EMR 98 vs. 98	EMR precutting vs. C-EMR 14.1 vs. 13.9	EMR precutting vs. C-EMR 87.8 vs. 67.3	EMR precutting vs. C-EMR 98.0 vs. 85.7	NR	EMR precutting vs. C-EMR 11.8 vs. 2.8	EMR precutting vs. C-EMR 1.0 vs. 1.0
Kim *et al* [64], 2013	Korea	Single-center, retrospective	03/2007 03/2011	1	3	91	91	20.9	51.6	61.5	0.0	30.0	6.5
Jung *et al* [65], 2018	Korea	Multicenter, prospective	01/2012 12/2013	5	NR	39	39	25.0	92.3	51.3	NR	26.8	12.8

Meta-analyses evaluating the efficacy and safety of EMR precutting

	Method	No. of studies included	Study design	No. of patients	Complete resection rate	*En bloc* resection rate	Recurrent/ residual polyp rate	Adverse event rate	Other outcomes
Fuccio *et al* [66], 2017	EMR precutting	12	3 prospective; 9 retrospective	694	Pooled rate: 60.6%, 95%CI 40.6-77.5	Pooled rate: 68.4%, 95%CI 51.7-81.3	Pooled rate 2.0%, 95%CI 0.7-5.6 at 12 months	Pooled rate 4.0%, 95%CI 2.8-5.8 for delayed bleeding Pooled rate 4.8%, 95%CI 2.4-9.1 for perforation Pooled rate 1.0%, 95%CI 0.4-2.3 for need for surgery	Higher R0 and *en bloc* resection rates in Asian countries

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Supplementary Table 1 *(Continued)*

Studies evaluating the efficacy and safety of EMR with band ligation

Author [Ref], year	Country	Study design	Study period	No. of centers	No. of endoscopists	No. of patients	No. polyps	Polyp size (mm)	Complete resection rate (%)	*En bloc* resection rate (%)	Recurrent/ residual polyps (%)	Total resection time*	Adverse event rate (%)
Ono *et al* [70], 2003	Japan	Single-center, prospective	01/1999 01/2002	1	NR	28	ESMR-L vs. C-EMR 14 vs.14	ESMR-L vs. C-EMR 7.3 vs.6.9	ESMR-L vs. C-EMR 100 vs.57	NR	ESMR-L vs. C-EMR 0.0 vs.0.0	NR	NR
Ebi *et al* [72], 2018	Japan	Dual-center, prospective	05/2003 06/2002	2	NR	33	ESMR-L vs. C-EMR 19 vs.14	ESMR-L vs. C-EMR 5.0 vs.6.9	ESMR-L vs. C-EMR 89.5 vs.50	ESMR-L vs. C-EMR 100 vs.100	ESMR-L vs. C-EMR 0.0 vs.0.0	ESMR-L vs. C-EMR 6min vs.6.5min	ESMR-L vs. C-EMR 0.0 vs.0.0
Kim *et al* [73], 2011	Korea	Multicenter, retrospective	01/2004 12/2010	4	NR	100	ESMR-L vs. C-EMR 45 vs.55	ESMR-L vs. C-EMR 5.9 vs.6.3	ESMR-L vs. C-EMR 100 vs.91	ESMR-L vs. C-EMR 93.3 vs.65.5	NR	ESMR-L vs. C-EMR 4.8min vs.5min	ESMR-L vs. C-EMR 4.4 vs.0.0
Lee *et al* [74], 2020	Korea	Single-center, retrospective	11/2011 07/2009	1	NR	139	ESMR-L vs. C-EMR 29 vs.110	ESMR-L vs. C-EMR 7.7 vs.6.8	ESMR-L vs. C-EMR 93.1 vs.74.5	ESMR-L vs. C-EMR 100 vs.94.5	NR	ESMR-L vs. C-EMR 10.7min vs.7.7min	ESMR-L vs. C-EMR 0.0 vs.0.0
Choi *et al* [76], 2013¶¶¶	Korea	Single-center, prospective	2008 2011	1	2	60	EMR-L vs. ESD 29 vs. 31	EMR-L vs. ESD 4.3 vs. 5.2	EMR-L vs. ESD 82.8 vs. 80.6	NR	NR	ESMR-L vs. C-EMR 6.3min vs.15.5min	ESMR-L vs. C-EMR 0.0 vs.3.2
Bang *et al* [78], 2016¶¶¶	Korea	Single-center, prospective	01/2012 02/2016	1	4	77	EMR-L vs. ESD 53 vs. 24	EMR-L vs. ESD 4.6 vs. 5.2	EMR-L vs. ESD 100 vs. 54.2	EMR-L vs. ESD 100 vs. 100	EMR-L vs. ESD 0.0 vs. 4.2	EMR-L vs. ESD 5.3min vs. 17.9 min	EMR-L vs. ESD 0.0 vs. 0.0
Lim *et al* [77], 2019¶¶¶	Korea	Single-center, retrospective	01/2011 12/2012	1	2	82	EMR-L vs. ESD 66 vs. 16	EMR-L vs. ESD 5.2 vs. 7.8	EMR-L vs. ESD 100 vs. 100	EMR-L vs. ESD 95.5 vs. 75	EMR-L vs. ESD 0.0 vs. 0.0	EMR-L vs. ESD 7.1min vs. 24.2 min	EMR-L vs. ESD 0.0 vs. 0.0

Meta-analysis comparing the effect of EMR with band ligation vs. ESD for rectal neuroendocrine tumors

Author, [Ref], year	Method vs. comparator	No. of studies included	Study design	No. of patients	Complete resection rate	*En bloc* resection rate	Recurrent/ residual polyp rate	Adverse event rate	Resection Time
Pan *et al* [79], 2018	EMR-L vs. ESD	14	2 prospective; 12 retrospective	823	OR 4.08, 95%CI 2.42-6.88	NR	OR 0.76, 95%CI 0.11-5.07	OR 0.56, 95%CI 0.28-1.14	MD -1.59, 95%CI -2.27 to -0.90

† statistically significant *: standard deviation or interquartile range; NR, not reported; ¶: study comparing outcomes of tip-in EMR vs. C-EMR; ¶¶; study comparing outcomes of EMR precutting vs. C-EMR; ¶¶¶: study comparing outcomes of EMR with ligation (EMR-L) vs. endoscopic submucosal dissection (ESD) for small (≤10 mm) rectal neuroendocrine tumors; OR, odds ratio; RR, relative risk; MD, mean difference; 95%CI, 95% confidence intervals

C-EMR, Conventional endoscopic mucosal resection; No., number