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## Indications and outcomes of endoscopic resection for non-pedunculated colorectal lesions: A narrative review

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### Abstract

In the last years, endoscopic techniques gained a crucial role in the treatment of colorectal flat lesions. At the same time, the importance of a reliable assessment of such lesions to predict the malignancy and the depth of invasion of the colonic wall emerged. The current unsolved dilemma about the endoscopic excision techniques concerns the necessity of a reliable submucosal invasive cancer assessment system that can stratify the risk of the post-procedural need for surgery. Accordingly, this narrative literature review aims to compare the available diagnostic strategies in predicting malignancy and to give a guide about the best techniques to employ. We performed a literature search using electronic databases (MEDLINE/PubMed, EMBASE, and Cochrane Library). We collected all articles about endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) registering the outcomes. Moreover, we analyzed all meta-analyses comparing EMR *vs* ESD outcomes for colorectal sessile or non-polypoid lesions of any size, preoperatively estimated as non-invasive. Seven meta-analysis studies, mainly Eastern, were included in the analysis comparing 124 studies and overall 22954 patients who underwent EMR and ESD procedures. Of these, eighty-two were retrospective, twenty-four perspective, nine case-control, and six cohorts, while three were randomized clinical trials. A total of 18118 EMR and 10379 ESD were completed for a whole of 28497 colorectal sessile or non-polypoid lesions > 5-10 mm in size. In conclusion, it is crucial to enhance the preoperative diagnostic workup, especially in deciding the most suitable endoscopic method for radical resection of flat colorectal lesions at risk of underlying malignancy. Additionally, the ESD necessitates further improvement because of the excessively time-consuming as well as the intraprocedural

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technical hindrances and related complications. We found a higher rate of *en bloc* resections and R0 for ESD than EMR for non-pedunculated colorectal lesions. Nevertheless, despite the lower local recurrence rates, ESD had greater perforation rates and needed lengthier procedural times. The prevailing risk for additional surgery in ESD rather than EMR for complications or oncologic reasons is still uncertain.

**Key Words:** Colorectal cancer; Adenoma detection; High-resolution colonoscopy; Chromoendoscopy; Pit pattern; Dysplasia

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**Core Tip:** The current unsolved dilemma concerns the necessity of a reliable submucosal invasive cancer assessment system, able to stratify the risk of the post-procedural need for surgery after endoscopic submucosal dissection of colorectal non-pedunculated lesions. It should be capable of selecting the at-risk subgroups of patients in whom endoscopic submucosal dissection could be the most suitable method. Accordingly, this narrative review aims to describe the best diagnostic strategies for predicting malignancy according to current endoscopic technology, to choose wisely among endoscopic mucosal resection, and endoscopic submucosal dissection procedures.

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## INTRODUCTION

The Japanese[1,2], European[3], and American[4,5] guidelines recommend that large sessile colorectal polyps and laterally spreading tumor (LST) can be successfully removed by piecemeal endoscopic mucosal resection (p-EMR)[2,3,5,6] if there are no signs of deep submucosal invasion on endoscopic assessment[5-9].

EMR is fast and safe to remove non-pedunculated colorectal lesions sized above 10-15 mm[1-3,5]. However, p-EMR may impair accurate histological assessment and has higher recurrence rates than *en bloc* resection[1-3,5], resulting in a higher frequency of post-procedural surgery[1-3,5].

*En bloc* EMR (with distinct techniques) for sessile polyps or LSTs  $\geq 20$  mm has been reported in 16%-48% of cases[10-14], with a success rate ranging from 42.9% to 98.8% and R0 rate between 45.0% to 96.7% cases[15-19]. A 2009 meta-analysis about endoscopic excision of large colorectal sessile polyps and LST lesions, reported an *en bloc* EMR rate of 62.85% and R0 rate of 58.66% on a sample of over 5221 patients[20]. It would be adequate to refer to the recurrence and surgery rates for EMR. Nevertheless, EMR is contraindicated in the presence of signs of deep invasion, like tissue ulceration/hardening, central depression, and non-lifting signs after submucosal injection[1-3,5].

Endoscopic submucosal dissection (ESD) should be preferred over EMR in cases of colorectal lesions greater than 20 mm with signs of superficial submucosal invasive cancer (SMIC), non-granular (NG) surface pattern, or when it could not be radically removed by the conventional procedures[2,5,21].

ESD achieves higher rates of *en bloc* and R0 resection, which translates into more adequate histological assessment and lower rates of local recurrence[1,2,5,22]. The downsides of ESD are longer procedural time and higher intraprocedural complications such as perforation, which of course are lowered by experience[1,2,5,21]. However, a recent systematic review has suggested limiting the indication for ESD because of the high incidence registered of non-curative resection due to a wrong SMIC assessment[2].

Colorectal lesion morphology can predict the risk of SMIC and help to guide the most appropriate endoscopic treatment[3,5,21,23]. Three parameters have to be considered: morphological pattern (MP) according to the Paris 2002 classification[24] and updated for the colon in the Kyoto 2008[25]; glandular pattern [pit pattern (PP)] according to the Kudo classification[26]; and vascular pattern[24,25,27-29]. The assessment of MP requires the use of a high-definition endoscope[21,24,25,27].

Diagnostic performance for the histological prediction of underlying malignancy of colorectal lesions according to their MP, as well as to Kudo PP, narrow-band imaging (NBI) international colorectal endoscopic (NICE), and Japanese NBI Expert Team (JNET) classifications are described in Table 1[6].

Regarding MP, Paris type 0-IIc non-polypoid lesions have a higher risk of SMIC than Paris 0-IIa, 0-IIb, and polypoid lesions[5,21,24,25,27]. Furthermore, the rates of SMIC for granular (G) homogenous, G nodular mixed, NG flat, and NG pseudodepressed LSTs were 4.9%, 15.9%, 3.0%, and 19.4%, respectively[30]. Additionally, the risk of occult SMIC according to colonic lesion morphology and location have been estimated to be 0.8% for 0-IIa G (proximal: 0.7%, distal: 1.2%), 7.1% for 0-IIa + Is G (proximal: 4.2%, distal: 10.1%), 3.7% for 0-Is G (proximal: 2.3%, distal: 5.7%), whereas SMIC risk was 4.2% for 0-IIa NG (proximal: 3.8%, distal: 6.4%), 14.1% for 0-IIa + Is NG (proximal: 12.7%, distal: 15.9%), 15.3% for 0-Is NG (proximal:12.3%, distal: 21.4%)[6]. Though those lesions without these features might still contain SMIC that is not visible on endoscopic inspection, which is defined as covert SMIC[6].

Current guidelines support the use of high-resolution colonoscopy with chromoendoscopy (dye or virtual) and optical magnification to establish the presence of SMIC and the feasibility of resection[24,25,26,31,32]. Virtual chromoendoscopy, by “real-time imaging” modifications (with NBI, flexible spectral imaging color enhancement, or i-Scan), allows the correct evaluation of PP and vascular pattern[5,21,24-26]. Optical magnification endoscopes identify the mucosal surface PP according to the Kudo classification[2,33].

The Japanese usually assess the risk of colorectal lesion infiltration by using chromoendoscopy with indigo carmine or crystal violet. In the Western areas, the reduced spread of magnification (both high costs and long procedural times) has restricted the evaluation of the risk of lesion infiltration to lifting-sign[3,21,26,34].

These techniques have improved the early detection of colorectal cancer (CRC) by characterizing the microscopic appearance of the dimples or furrows that separate the mucosal cells, which change according to the distinct stages of dysplasia and neoplastic transformation[5,21,24,26,34]. Specifically, the sensitivity and specificity for the diagnosis of T1 CRC with deep SMIC by using NBI were 79% and 94%, respectively[35].

## NICE CLASSIFICATION

The employment of NBI[36,37] has led to NICE classification[38] that distinguishes among hyperplastic polyps (type 1), adenomas (type 2) with/without superficial SMIC, and cancers with deep SMIC (type 3) based on color features, vessels, and surface pattern[38-40].

Therefore, lesions with glandular distortion but intact vascular structures [Kudo Vi, NICE type 2] are at risk of a superficial SMIC and are suitable for endoscopic *en bloc* resection. Whereas a highly distorted PP or an absence/irregularity of the submucosal vessels (Kudo Vn or NICE type 3) are strongly predictive of deep SMIC. Therefore, after performing biopsies and tattoos of the lesion, surgical treatment should be judged[38].

The sensitivity, specificity, positive predictive value, and negative predictive value of the NICE classification for predicting deep SMIC were 58.4% (95% confidence interval (CI): 47.5%-68.8%), 96.4% (95%CI: 95.5%-97.2%), 41.6%, (95%CI: 32.9%-50.8%), and 98.1% (95%CI: 97.5%-98.7%), respectively[39], whereas 99.1%, 57.7%, 95.4%, and 88.2%, respectively in differentiating neoplastic from non-neoplastic polyps[40]. Interobserver agreement was relevant (kappa: 0.70) for predicting deep SMIC[41]. Also, the sensitivity for the diagnosis of deep SMIC regarding lesions with type 3 of NICE was significantly greater among very expert endoscopists than in the less-experienced ones (91.7% *vs* 83.3%; *P* = 0.04)[42].

**Table 1** Diagnostic performance for the histological prediction of underlying malignancy of colorectal lesions according to their morphological pattern as well as to Kudo pit pattern, narrow-band imaging international colorectal endoscopic, and Japan narrow-band imaging expert team classifications

Variables	Sensitivity	Specificity	PPV	NPV	Accuracy
<b>Morphological pattern<sup>1</sup></b>					
0-IIa G	5.7%	70.0%	1.7%	89.1%	64.6%
0-Is G	11.5%	83.2%	5.8%	91.2%	77.3%
0-IIa + Is G	22.9%	77.4%	8.4%	91.7%	72.8%
0-IIa NG	27.4%	79.5%	10.8%	92.4%	75.2%
0-Is NG	16.6%	95.5%	25.0%	92.7%	89.0%
0-IIa + Is NG	15.9%	94.5%	20.7%	92.6%	88.0%
<b>Kudo pit pattern (NBI)<sup>2</sup></b>	73.3%-93.7% <sup>3</sup>	89.2%-100% <sup>3</sup>	93.7%-100% <sup>3</sup>	89.2%- 96.4% <sup>3</sup>	92.0%-96.7% <sup>3</sup>
<b>NICE classification<sup>4</sup></b>					
Type 1	82.1%-84.6%	93.8%-94.9%	65.9%-92.5%	60.4-98.2%	93.9%-97.8%
Type 2	89.8%-91.4%	84.3%-86.3%	89.1%-90.7%	97.3-97.7%	56.6%-61.2%
Type 3	83.3%-91.7%	96.4%-97.0%	96.0%-96.8%	45.8-54.0%	99.4%-99.7%
<b>JNET classification<sup>5</sup></b>					
Type 1	73.0%-87.1%	96.0%-99.5%	73.4%-92.3%	96%-98.9%	93.0%-98.5%
Type 2A	82.5%-96.0%	70.0%-91.1%	90.3%-96.7%	62.1%-92.1%	84.5%-90.9%
Type 2B	42.0%-75.6%	84.2%-95.0%	26.0%-67.3%	92.2%-98.0%	81.3%-93.0%
Type 3	35.0%-91.7%	98.1%-100%	63.2%-100%	93.8%-99.7%	94.0%-98.0%

<sup>1</sup>Diagnostic performance of lesion classification types according to Paris classification for covert submucosal invasive cancer (SMIC) (SMIC that is not visible on endoscopic inspection).

<sup>2</sup>Narrow-band imaging.

<sup>3</sup>These percentages refer to the ability of preoperative magnifying chromoendoscopy (Kudo pit pattern classification by narrow-band imaging assessment of mucosal surface) to predict depth of submucosal invasion for large colorectal lesions.

<sup>4</sup>Narrow-band imaging international colorectal endoscopic (NICE) classification, NICE type 1: hyperplastic polyps, NICE type 2: adenomas (with/without risk of a superficial SMIC), NICE type 3: strongly predictive of cancers with deep SMIC.

<sup>5</sup>Japan narrow-band imaging expert team classification (JNET), JNET type 1: predictive of hyperplastic/sessile serrated polyps, JNET type 2A: predictive of neoplasia with low/high-grade intramucosal neoplasia, JNET type 2B: predictive of high-grade intramucosal neoplasia/shallow submucosal invasive cancer, JNET type 3: predictive of cancer with deep SMIC. PPV: Positive predictive value; NPV: Negative predictive value; NBI: Narrow-band imaging; JNET: Japan Narrow-band imaging expert team classification; NICE: Narrow-band imaging international colorectal endoscopic; NG: Non-granular; G: Granular.

## JNET CLASSIFICATION

The JNET classification consists of four categories and uses vascular pattern and MP to diagnose hyperplastic/sessile serrated polyps (type 1), neoplasia with low/high-grade intramucosal neoplasia (type 2A), high-grade intramucosal neoplasia/shallow SMIC (type 2B), and cancer with deep SMIC (type 3)[42-46]. The interobserver and the intraobserver agreement for the JNET classification were moderate (kappa: 0.52) and excellent (kappa: 0.88), respectively. Type 2B lesions included a variety of colorectal tumors, including those with high-grade dysplasia, with superficial and deep SMIC [45]. Both non-expert/expert endoscopists had similar specificity, negative predictive value, and accuracy (> 90%) for 1/2B/3 types and sensitivity and positive predictive value above 90% for type 2A, whereas type 2B exhibited a sensitivity of only 42%[44].

Colorectal polyps exhibiting ulceration, excavation, defined deep depression, Paris IIc and IIa+c, mucosal friability, convergent plicae, and Kudo type V PP most likely correspond to SMIC. Therefore, they are at high risk for lymphovascular invasion and lymph node metastasis[48-52].

Additionally, superficial SMIC (sm1 and sm2, involving the upper and middle level of the submucosa, respectively)[25] was not closely associated with non-lifting signs because underlying undamaged submucosa may still expand, unlike deep SMIC (sm3, involving the lower level of the submucosa)[25,53-55]. Accordingly, when deep SMIC

is suspected or proven, in addition to excision of the lesion, the removal of the loco-regional lymph nodes is necessary, which can only be achieved by surgery[5,21,26,25,52].

Moreover, staging even with echoendoscopy and magnetic resonance imaging can be considered for rectal tumors with endoscopic features suspected for SMIC and eventually lymph node staging[56,57]. Colorectal surgery is recommended for lymphovascular invasion, SMIC deeper than sm1, positive/non-evaluable vertical margins, or poorly differentiated tumor[8,21,26,24,25]. When a positivity of horizontal margin is shown without additional high-risk criteria, endoscopic surveillance/re-treatment could be weighed instead of surgery[21,26,24,25].

### **EMR en bloc or piecemeal: indications, efficacy, and safety**

On the other hand, colorectal lesions without SMIC-suggestive features have a high likelihood of being radically removed by endoscopic techniques and should not be referred for surgery without primary estimating the possibility of a polypectomy/EMR at an expert endoscopy center[58]. Moreover, it should be avoided to perform biopsies in such lesions because it can produce submucosal fibrosis, not allowing the lifting process[5,21,25,26,34]. Indeed, in a study[59] of 36 patients with 38 large polypoid lesions, negative for cancer who were referred from a colorectal surgeon to an EMR expert, 79% of the lesions were successfully treated endoscopically, thus avoiding unnecessary surgery in 71% of cases.

EMR encompasses different techniques (*i.e.* inject and cut, with either cold or hot snare; cap-assisted; underwater; hybrid)[32,60-63]. Various studies have proved that *en bloc* or p-EMR can radically and safely remove most colorectal sessile or non-polypoid lesions[13-16,64].

*En bloc* or p-EMR resections aim particularly at a resection with a histologically confirmed negative resection margin. Particularly, *en bloc* R0 resection, together with the absence of undifferentiated adenocarcinoma, deep invasion (submucosal invasion > 1000  $\mu$ m), and lymphovascular invasion excludes the risk of lymph node metastasis [2,3,5,7,8,10-16,52,64].

Specifically, *en bloc* EMR has been reached in 47.2%[15], 53.5%[11], 66.3%[14], 91.3%[17], and 98.8%[16] of procedures, whereas R0 was achieved in 45%[14], 88.9%[15], 89.2%[10], 91.0%[11], and 96.7%[18] of events for colorectal sessile polyps and/or LSTs [14,15,17,18] or for recurrent adenomas after p-EMR[11] of various diameters ( $\geq 10/20$  mm[10,14,17], ranging 8-100 mm[11], 10-50 mm[18], or 20-50 mm[14]).

According to current guidelines, p-EMR is mainly employed for treating large non-malignant colorectal sessile or non-polypoid lesions[3,63,65]. To be optimally performed, it requires the resection to be completed by a limited number of pieces and adequate margins[2,3,5].

However, according to a meta-analysis published in 2016[65] including 6442 patients and 6779 large colorectal polyps, successful endoscopic resection (independently from surgery following endoscopy and, in some events, to histology) by any endoscopic technique, post-endoscopic resection bleeding, perforation, and mortality occurred in 96.3% (95%CI: 96.0%-97.0%), 6.5% (95%CI: 5.9%-7.1%), 1.5% (95%CI: 1.2%-1.7%), and 0.08% cases (95%CI: 0.01%-0.15%), respectively, after resection. A rate of 8% of patients (95%CI: 7%-10%,  $I^2 = 78.6\%$ ) underwent surgery due to non-curative endoscopic resection and 1.0% (95%CI: 0.7%-1.4%,  $I^2 = 0\%$ ) due to adverse events[65].

Other studies have also reported various percentages of post-EMR bleeding in 0% [14,16,19], 1.75% [18], 2.8%-3.1% [13], 6.2% [66], 9.8% [11], and 10.8% [12] after the resection of large colorectal lesions.

The efficacy and safety of hot and cold snare EMR for non-pedunculated colorectal adenomas < 20 mm has been evaluated in few studies, which suggested a capacity for resectability improvement and for delivering better histopathological evaluation especially with the cold snare technique[15,67-69].

Besides, a Japanese single-armed multicenter prospective trial[67] of 624 patients undergoing standard EMR of non-pedunculated polyps with a diameter  $\leq 20$  mm, successful *en bloc* and R0 resection rates of 93.3% and 78.3%, respectively, were observed. Postoperative rates of bleeding and perforation were 1.1% and 0%, respectively[67].

Another Japanese multicenter randomized controlled trial (Yamashina *et al*[68], 2019) showed for 102 sessile lesions ranging between 10-20 mm and treated by standard EMR (with electrocautery) an *en bloc* resection of 75% (95%CI: 65%-83%), R0 resection of 50% (95%CI: 40%-60%), with a median procedure time of 175 s, and adverse events were reported in 2% of cases.

A Japanese prospective, observational study[69] assessing an overall 80 non-pedunculated adenomas measuring 10-14 mm and treated with cold snare EMR

reported *en bloc* and R0 resection rates of 82.5% and 63.8%, respectively. No post-procedural adverse events occurred.

Otherwise, in a retrospective, single-center study[15] analyzing 44 EMR salvage procedures (following the previous p-EMR) of polyps whose median size was 14 mm, *en bloc* resection rate was 15.9%, R0 resection rate was 31.8%, and intraprocedural argon plasma coagulation (APC) ablation of visible residual was 65.9%. Bleeding occurred in 4.5%, and there were no perforation events[15].

Among the studies evaluating EMR for colorectal lesions < 20 mm, the majority did not analyze the recurrence rates[67-69], but only one reported a 39.4% of recurrence at surveillance[15].

Hot snare EMR is the conventional technique employed for resection of large ( $\geq 20$  mm) non-malignant sessile colonic polyps, although severe adverse events can occur mainly due to electrocautery application.

Cold snare p-EMR of sessile colonic polyps or LSTs  $\geq 20$  mm represents an alternative technique feasible, efficient, and secure in many cases, although large randomized/prospective trials to strengthen the results and to define which polyps are rightly suitable for this method are needed. Furthermore, the adverse event and polyp recurrence rates are usually low.

A retrospective study[70] reported similar technical success for both cold snare p-EMR and standard EMR employed for 156 and 406 sessile serrated lesions sized  $\geq 20$  mm (100% *vs* 99%;  $P =$  not significant), respectively. While cold snare p-EMR was not associated with adverse events, delayed bleeding and deep mural injury were observed in 5.1% and 3.4%, respectively, following EMR[70].

A retrospective Australian study[71] of 186 patients treated by cold snare p-EMR for 204 sessile polyps  $\geq 20$  mm reached a median interval of 150 d of residual/recurrent polyp in 5.5% of cases, whereas at a median interval-time of 18 mo registered a 3.5% late residual/recurrent polyp. Bleeding occurred throughout the p-EMR in 2.2% of cases, whereas post-EMR bleeding occurred in 3.8%[71].

In a prospective observational cohort study[72], the risk of residual or recurring adenoma after p-EMR of large non-pedunculated polyps was 10.8% (mean size,  $31.6 \pm 10.1$  mm)[72].

A prospective and multicenter Australian study[73] on 1178 LSTs  $\geq 20$  mm removed by p-EMR showed a recurrence rate of 19.4%[73]. In detail, LST size  $\geq 40$  mm [odds ratio (OR) = 2.47;  $P < 0.001$ ], the intraprocedural bleeding (OR = 1.78;  $P = 0.024$ ), and high-grade dysplasia (OR = 1.72;  $P = 0.029$ ) were independent predictors for polyp recurrence[73].

### **Indications, outcomes, and adverse events of underwater EMR**

Principal boundaries with conventional EMR involve high percentages of polyp recurrence and low *en bloc* resection rates, especially for lesions sized above 20 mm. Underwater EMR (U-EMR) represents an alternative method for *en bloc* resection of more extensive lesions. Comparison studies showed the feasibility and safety of U-EMR that is associated with higher *en bloc* and R0 resection rates for colonic lesions compared to standard EMR[62].

Previously, Binmoeller *et al*[13], in a prospective observational study, reported a 100% R0 resection concerning U-EMR for large sessile polyps, and delayed bleeding occurred in 5%[13].

In a multicenter randomized controlled trial[68], U-EMR for polyps with intermediate-size (10-20 mm in diameter) demonstrated higher *en bloc* and R0 resection rates as compared to conventional EMR [89% (95%CI: 81%-94%) *vs* 75% (95%CI: 65%-83%),  $P = 0.007$ ; and 69% (95%CI: 59%-77%), *vs* 50% (95%CI: 40%-60%),  $P = 0.011$ , respectively]. There was no significant difference in prevalence of adverse events in the U-EMR group (2.8% *vs* 2.0%,  $P =$  not significant)[68].

In a meta-analysis of American and European studies[74], the U-EMR technique exhibited an R0 resection rate of 96.36% (95%CI: 91.77%-98.44%). Also, *en bloc* resection rate was described in 57.07% (95%CI: 43.20%-69.91%) for sessile polyps and non-polypoid lesions (mean size range, 15.0-33.8 mm). Adverse events occurred in 3.31% (95%CI: 1.97%-5.52%) and late bleedings in 2.85% (95%CI: 1.64-4.90%), in the absence of perforation[74].

In a recent systematic review and meta-analysis[75], U-EMR has shown a higher *en bloc* resection rate than conventional EMR for removing polyps > 20 mm in size (OR = 1.9; 95%CI: 1.0-3.5;  $P = 0.04$ ), whereas R0 resection (OR = 3.1; 95%CI: 0.7%-12.6%;  $P = 0.14$ ), piecemeal resection (OR = 3.1; 95%CI: 0.7%-12.6%;  $P = 0.13$ ), and diagnostic accuracy for CRC (OR = 1.1; 95%CI: 0.6%-1.8%;  $P = 0.82$ ) were similar. There were lower rates of recurrence (OR = 0.3; 95%CI: 0.1%-0.8%;  $P = 0.01$ ) and incomplete resection (OR = 0.4; 95%CI: 0.2%-0.5%;  $P = 0.001$ ) with U-EMR. The two methods

produced equivalent procedural times and safety profiles.

### **Indications and outcomes of cap-assisted EMR and EMR with a ligation device**

The cap-assisted EMR (C-EMR) and EMR with a ligation device (EMR-L) in the colon have limited indications, especially for R0 resection of small rectal neuroendocrine tumors (NETs) because their radical removal can be difficult to achieve with standard endoscopic resection techniques due to the frequent involvement of the submucosal layer[76,77].

Some articles have described the usefulness of a distally attached cap during colonoscopy for shortening cecal intubation, decreasing patient discomfort, improving adenoma detection rate, and simplifying mucosal resection of non-pedunculated lesions[81-85]. Moreover, C-EMR can resect more adequately complex and large inter-plicae non-polypoid lesions, especially those located in the right colon[18].

A 2011 single-center prospective, randomized, controlled trial[86] showed during C-EMR/colonoscopy of 166 patients a significantly reduced procedural time ( $3.5 \pm 4.5$  vs  $4.2 \pm 5.1$  min,  $P = 0.010$ ), a higher polyp detection rate ( $3.4 \pm 2.7$  vs  $2.7 \pm 1.9$ ,  $P = 0.003$ ), and a lower rate of missed polyps ( $1.1 \pm 1.5$  vs  $0.8 \pm 0.9$ ,  $P = 0.024$ ) than patients undergoing conventional colonoscopy[86].

As reported in a retrospective study[87], C-EMR was feasible for resection of small rectal NETs. This study analyzed a total of 34 rectal NETs that were removed by C-EMR, reaching a higher R0 resection rate ( $94.1\%$  vs  $76.8\%$ ,  $P = 0.032$ ) and a higher tendency of frequency of intraprocedural bleeding ( $8.8\%$  vs  $0\%$ ,  $P = 0.051$ ) than standard EMR ( $n = 56$ ); the procedural time was significantly shorter in the C-EMR group ( $3.9 \pm 1.1$  vs  $19.0 \pm 12.1$  min,  $P < 0.001$ ) than the ESD group ( $n = 32$ )[87]. For NETs ranging 6-8 mm in size, there were no differences in the adverse events or R0 resection rates between the C-EMR group and ESD group.

A review[88] suggested that C-EMR is effective and safe when polyp removal is challenging *via* standard EMR technique. Specifically, this study described a rate of 100% R0 resection after C-EMR of 21 ileocecal valve polyps (median size, 15 mm), and late bleeding occurred in 4.8%[88].

On the other hand, a Japanese and retrospective study[89] evaluating 22 colorectal carcinoid tumors (mean size, 6.2 mm) that were treated by EMR-L reported *en bloc* and R0 resection rates of 73% and 50%, respectively, for EMR-L. Perforation and bleeding did not occur[89].

Finally, the authors of a recent retrospective Korean study[90] deduced that EMR-L may be the preferred treatment method for small rectal NETs, considering the higher *en bloc* resection rate in the EMR-L group than C-EMR one ( $100\%$  vs  $92.9\%$ ,  $P = 0.003$ ). Though only a superior trend for R0 resection rate was observed in the former group ( $92.5\%$  vs  $83.3\%$ ,  $P = 0.087$ ), and there were no differences in intraprocedural adverse events ( $P = 0.870$ )[90].

### **Risk factors for adverse outcomes and recurrences after EMR of colorectal lesions > 20 mm**

The factors that limit EMR[91] are resection technique[92,93], polyp size[94,95], previous removal attempts[96], location[97], endoscopist experience, and patient comorbidities[91,95,96,97].

Indeed, the risk factors for post-procedural hemorrhage included polyp location in the proximal tract[66,98,99,100] and particularly those larger than 40 mm[101,102]. Perforation occurred unusually (0.36%-6.30%)[12-14,98,103] and was higher particularly for lesions of the transverse colon with underlying high-grade dysplasia, SMIC, and after *en bloc* resection[3].

In detail, the perforation event has complicated endoscopic procedures in 0%[12, 13], 0.36%[11], 1.4%-1.5%[98,103], 1.75%[18], 1.5%-1.9%[16], 2.9%[19], and 6.3%[14] of cases, with a negligible procedure-related fatality ( $< 0.1\%$ )[12-14,18,19]. Late bleeding was usually endoscopically managed, while prophylactic coagulation of visible vessels or clip use did not lessen the risk of bleeding[1,3,6,50].

Also, complex lesions located at the ileocecal valve (single and both lips) were associated with resection failures (OR = 12.2; 95%CI: 1.64%-90.50%;  $P = 0.002$ ) as well as in cases of terminal ileal involvement (OR = 121.3; 95%CI: 1.52%-84.00%;  $P = 0.002$ )[97]. The appendiceal orifice, the anorectal junction, and the peridiverticular sites have also been considered challenging to remove the lesions safely[2,3,5,10,98].

Additionally, an American study identified the previous resection attempts as a significant risk factor for failure of complete excision (OR = 0.024;  $P = 0.001$ ) and for achieving a successful resection without applying thermal ablation of residual (OR = 0.081;  $P < 0.001$ )[96].

Moreover, no study has defined the threshold extent for which *en bloc* EMR is unsafe. *En bloc* EMR is generally limited to lesions sized up to 20 mm, while the larger usually require ESD or surgery for local radicality[5,7,21,20,32]. Specifically, for sessile polyps and flat lesions, the maximum size to perform safely *en bloc* excision was 15-20 mm proximal to the splenic flexure where the risk of perforation is the greatest and 20-25 mm in the sigmoid/rectum tract for anatomic reasons[3,5,20,32].

Interestingly, the circumferential incision of lesions with hybrid ESD methods (*i.e.* cap-assisted or precut-EMR) can allow the extension of the size threshold for complete resection while reducing the risk of perforation[19,99,104,105].

Hence, the cases including sessile colorectal polyps  $\geq 20$  mm (Paris classification 0-IIa, 0-Is, 0-Isp), LSTs, lesions located in difficult areas, or colitis-associated dysplasia have been judged amenable to be referred to experienced endoscopists in a high volume tertiary referral center before surgical option[2,3,5,11].

The EMR treatment for large colorectal sessile or non-polypoid lesions is associated with heterogeneous rates of adenoma recurrence/persistence that range between 0% and 39.4%[74,106-108], depending on the EMR technique (*i.e.* standard, hybrid, cap-assisted, or underwater), polyp size/histology, a higher number of resected pieces, previous attempts of resection, and surveillance period (3-6 mo or  $\geq 12$  mo)[19,61,63,96,109].

Recurrence rates succeeding cold snare p-EMR were similar to standard EMR at two consecutive surveillances (4.3%/2.0% *vs* 4.6%/1.2%, respectively)[70].

Previously, Kikuchi *et al*[106] evaluated the risk of recurrence even in patients with CRC and SMIC of any size following EMR; none of the 17 patients with superficial SMIC registered localized recurrence or lymph node metastases.

Bergmann and Beger[18] showed a 3.3% local recurrence after treating lesions with sizes ranging from 10-50 mm. Notably, Masci *et al*[16] described an approximately 15% recurrence rate of the lesions either in high- or low-volume centers.

Specifically, a meta-analysis[65] including 6442 patients treated with endoscopic resection of 6779 large polyps found an endoscopic recurrence in 13.8% of cases.

Moss *et al*[17], Conio *et al*[12], and Buchner *et al*[11] showed adenomatous recurrence at the resection site in 16%, 21.9%, and 27%, respectively, for large sessile polyps or LST lesions, referred to using EMR.

Pohl *et al*[109] reported a 17.3% incomplete resection by using hot snare EMR for large lesions. On the other hand, Thoguluva *et al*[64] observed after cold snare EMR of intermediate-size non-polypoid lesions an overall residual disease in 4.1%, whereas Muniraj *et al*[63] reported 20% of recurrences at 6 mo. Additionally, Rex *et al*[108] displayed a comparable residual polyp rate after the EMR of large sessile serrated adenoma/polyps or traditional adenomas (8.7% *vs* 11.1%, respectively).

Non-standard EMR techniques have reported favorable outcomes regarding reducing residual or recurrence lesions[15,74,87,107]. Indeed, Hong *et al*[14], reported no recurrence after EMR with circumferential incision for the treatment of large sessile polyps and LSTs. Yang *et al*[87] observed no recurrence in the C-EMR group after resection of 34 small rectal NETs. Binmoeller *et al*[13] and Spadaccini *et al*[74] showed a recurrence rate of 1.8% and 8.8%, respectively, using U-EMR for sessile polyps and non-polypoid lesions at surveillance program. In contrast, Kim *et al*[15] displayed a significantly lower recurrence in the U-EMR group than the standard EMR (10.0% *vs* 39.4%). Instead, a 4% recurrence was described after the employment of C-EMR for sessile lesions (or LSTs) over 1 year of surveillance[107].

P-EMR has been judged as an independent risk factor for recurrence after endoscopic resection of non-pedunculated colorectal adenomas and early carcinomas [110].

In detail, Kim *et al*[111] observed at surveillance following the previous p-EMR of large non-pedunculated adenomas, a second and third recurrence in 34% and 20% among 70 recurrent lesions, respectively. Nevertheless, another study[19] recorded a surprisingly higher recurrence rate for standard EMR than p-EMR (25.9% *vs* 3.2%). Moreover, Kim *et al*[96] presented significantly diverse recurrence rates in the patients without any prior manipulation (7.7%), with previous biopsy sampling (40.7%), and with advanced manipulation (53.8%) identifying previous resection attempts as a significant risk factor compared with non-manipulated lesions (OR = 18.8;  $P = 0.001$ ). Besides, Nanda *et al*[97] showed for the lesions located in technically complicated sites such as ileum with/without valve involvement, an early and a late recurrence in 17.5% and 4.5% of patients, respectively.

Fortunately, most of such events are not an overwhelming barrier because they can be managed with further endoscopic therapy[107,112-115] when it is carried out with a regular surveillance program (3-6 mo) following the index endoscopy[3,5,32]. These relapses have been removed even with a 93% success rate for advanced colonic

adenomas up to 120 mm in size after conventional or wide-field EMR[10,17].

Thermal ablation/APC of margins at the resection site can be either an adjuvant treatment to clean suspicious margins to reduce recurrences or a subsequent therapeutic aid to eliminate the visible residual unresected after index EMR[21,23,114,115].

Renewed endoscopic treatment of recurrences is correlated with high curative rates, low complication rates, and a low risk of malignant evolution[111,112,115].

Brooker *et al*[112] showed a decrease of 50% of early relapse of large colorectal sessile polyps after combining EMR treatment with APC. The study by Kim *et al*[111] analyzing 70 recurrent lesions after the previous p-EMR of large non-pedunculated adenomas reported that 1 patient underwent surgery for an adenoma involving the ileocecal valve and another one underwent curative surgery for a deep SMIC. The rest of the patients were successfully managed endoscopically.

Furthermore, a recent large Australian randomized multicenter study (390 patients) of tertiary centers[115] confirmed reduced adenoma recurrence rates at early follow-up in patients treated with thermal ablation of the resection margins after the EMR of large LSTs as compared to controls without additional treatment (5.2% *vs* 21.0%, respectively). Otherwise, a small cohort Polish study[114] reported similar recurrence rates for large sessile polyps treated with both p-EMR and APC than those treated with only p-EMR (14% for both groups).

### **ESD: Indications, efficacy, safety, and recurrences**

The endoscopic eradication of colorectal preneoplastic and neoplastic lesions has continuously changed and evolved in the last decades to develop ESD[116-119], a more challenging technique[5,21,26,91,120]. The ESD method was initially developed in Japan in the early 2000s for the resection of superficial carcinomas of the upper digestive tract[121-124], whereas Western areas used ESD especially for treating colorectal lesions[4,5,21,26,91]. However, the technical difficulty, the necessity for a lengthy training of the medical/nursing team, and the higher complication rate than conventional EMR have hampered widespread adoption in Western countries[1,2,5,21].

ESD can have both a diagnostic and therapeutic intent, although due to higher rates of perforation the diagnostic intent in the colon is limited[1,2,5,21]. This procedure aims at the *en bloc* and deep removal of large non-pedunculated lesions with a high potential of malignancy. These lesions need an accurate histological assessment for the risk of lymph node metastases, and *en bloc* R0 is mandatory in these cases with high suspicion of superficial submucosal invasion[5,21,22,52].

ESD uses dedicated needles that by cutting the mucosa and submucosa can enable an almost surgical resection of lesions > 20 mm that are otherwise not radically removable or only in several fragments, providing a lower recurrence rate of the lesions[1,2,5,21].

The Japan Gastroenterological Endoscopy Society[21], European Society of Gastrointestinal Endoscopy[2], and American Society for Gastrointestinal Endoscopy [5] guidelines were endorsed to provide specific recommendations on the appropriate use of ESD. These guidelines strongly advise ESD instead of EMR in the following cases[1,2,5,21,106]: for the removal of large sessile or non-polypoid tumors (including LST G and nodular mixed types) assumed to have superficial SMIC, carcinoma with shallow T1 SMIC, depressed or irregular type tumors, LSTs (pseudo-depressed) with an NG surface pattern, Kudo Vi-type PP, when regardless of the size a lesion is radically unresectable with snare EMR, tumors with submucosal fibrosis, local residual or recurrent early carcinomas after inefficient endoscopic resection, or non-polypoid dysplasia/sporadic tumors in patients with inflammatory bowel disease.

Some studies have documented the efficacy and safety of ESD for treating sessile or non-polypoid lesions of any size, especially in Asian countries[5,123,125].

However, ESD has been complicated by late bleeding in 2% [123], 5% [125], 5.1%, and 13% [127] and by perforation in 2.5% [123], 3.2% [126], 4% [125], 7% [125], and 18% [127] of the procedures. Recurrence occurred in 4% [125], 7% [123], 7.5% [126], and 13.8% [65] of cases.

Specifically, a systematic review by Repici *et al*[128] evaluated, among 22 studies (91% Asian), the outcomes of 2841 sessile lesions or LSTs of any diameter [median of mean size, 32.4 mm (range 6.2-43.6 mm)] following ESD treatment. The *en bloc* and R0 rates were 91.6% and 88%, respectively, and significantly higher for Asians than Europeans (88% *vs* 65%, respectively) with a good safety profile (4% and 2% of the procedures were complicated by perforation or late bleeding, respectively). Furthermore, ESD showed a relapse rate of < 0.1%, whereas the estimation of surgery for complications was 1% [128].

A retrospective Japanese study[123] analyzed 1017 ESD procedures performed for sessile or non-polypoid lesions (mean size, 38 mm). *En bloc* resection was successful in 90% while R0 in 77% of cases[123]. Perforation and delayed bleeding rates were 2.5% and 2.0%, respectively. Relapses occurred in 7.5%[123]. A small prospective study[127] evaluating ESD outcomes in a French cohort of 45 patients (treated for sessile rectal tumors or LSTs  $\geq 10$  mm) showed fair *en bloc* resection rates (64%) as well as low curative R0 (53%). The complication rate was high (18% for perforation and 13% for late bleeding), while 7% relapsed during surveillance[127].

Another Japanese study[126] suggested the safety of ESD for treating early CRC; among the 373 analyzed patients, 82.4% had non-polypoid lesions and 17.3% sessile lesions (sized  $28.6 \pm 14.2$  mm). Post-procedural perforation and bleeding rates occurred in 3.2% and 5.1% of cases, respectively.

A retrospective Japanese study[93] compared EMR and ESD techniques for treating 189 large tumors (including LST-G/LST-NG, and depressed/protruded lesions). Despite the ESD group had significantly larger tumor sizes ( $31.6 \pm 9.0$  vs  $25.5 \pm 6.8$  mm,  $P < 0.001$ ), longer procedural times ( $87.2 \pm 49.7$  vs  $29.4 \pm 26.1$  min,  $P < 0.001$ ), and higher perforation cases (5.9% vs 0%,  $P = 0.04$ ), there occurred higher *en bloc* resection rates (83.5% vs 48.1%,  $P < 0.001$ ) and fewer recurrences (1.2% vs 15.4%,  $P = 0.002$ ) than EMR. Postoperative bleedings were similar in the two groups (2.4% vs 2.9%,  $P =$  not significant)[93].

A systematic review[125] of 15 European studies determined the efficacy and safety of ESD for treating 1404 cases with large and complex lesions [mean size, 40 mm (range 24-59 mm)]. The *en bloc* resection rate was 83%, and the R0 rate was 70%[125]. Perforation and bleeding rates were 7% and 5%, respectively. The recurrence rate was 4% in a year of surveillance time[125].

Notably, in the presence of residual or locally recurrent lesions after previous EMR, a new variant of the ESD technique using double clip and rubber band traction has shown promising results, either for removing LSTs deeply invading appendiceal orifice[129-131] or recurrent sessile serrated adenomas invading the site of previous appendectomy[132,133]. Indeed, in a retrospective French study[129], ESD with double clip and rubber band traction of 53 residual/locally recurrent colonic lesions achieved *en bloc* and R0 resections in 92.5% and 79.2%, respectively. Intraoperative perforations and late bleeding occurred in 7.5% and 1.9%, respectively, although they were endoscopically managed. No complications requiring surgery occurred[129].

Nevertheless, following the limited ESD indications[1,2,5,21] and the greater attention on the indiscriminate use of this procedure are the results of the systematic review by Fuccio *et al*[22] published in 2018 of mixed Asian and European (51 included) studies[22]. Of the 11260 lesions treated with ESD, 82.2% were adenomas with low or high-grade dysplasia. Submucosal cancers were in 15.7% of cases, but only 8% had superficial SMIC. This percentage was reduced to 6% when the analysis was limited to oncologically curative events, with no statistically significant difference between the European and Asian studies. Therefore, most lesions could have been radically resected, even with p-EMR. This study considered even the clinical outcomes of standard ESD performed on 18764 lesions (of 97 studies). The rates of *en bloc* resection and R0 were 91% and 82%, respectively, with a 2% recurrence rate[22]. European studies, as compared to Asian ones, displayed lower R0 rates (71.3% vs 86.6%) and a higher incidence of adverse events. Late bleeding and perforation occurred in 4.2%/8.6% vs 2.4%/4.5%, respectively, thus confirming greater expertise of Eastern endoscopist[116].

Therefore, the unsolved question concerns the necessity of a reliable SMIC assessment system, able to stratify the risk of the post-procedural need for surgery after ESD. In other words, it should be capable of selecting the at-risk subgroups of patients in whom ESD could be the most suitable method. Accordingly, this narrative review aims to describe the best diagnostic strategies for predicting malignancy based on the morphologic features of colorectal non-pedunculated lesions according to current endoscopic technology, to wisely choose among EMR and ESD procedures.

### **Inclusion criteria**

We included studies that assessed the morphological and imaging patterns predictive of SMIC of non-pedunculated colorectal lesions of any size before choosing among EMR or ESD procedures. We also included those studies comparing the two strategies, regardless of the techniques or devices employed.

### **Exclusion criteria**

We excluded studies including colorectal lesions removed in patients with inflammatory bowel disease and those using surgery as a control group.

**EMR vs ESD: Systematic reviews and meta-analyses**

**En bloc and R0:** As shown in Table 2, a systematic review and meta-analysis[134], including four retrospective studies and 243 Asiatic patients, reported a significantly higher percentage of *en bloc* resection for sessile polyps (rectal carcinoids < 15 mm) in ESD than EMR group (100% vs 92%, respectively) and also a higher R0 of 87.7% than 69.1% (OR = 0.29; 95%CI: 0.14–0.58;  $P < 0.001$ ), respectively.

A meta-analysis of six case-control studies[135] of Asian populations, including 893 patients treated for sessile or flat lesions  $\geq 10$  mm, reported a higher *en bloc* resection rate in the ESD group than the EMR group (87.9% vs 44.5%, respectively; OR = 7.94; 95%CI: 3.96-15.91;  $P < 0.001$ ). Also, the ESD and EMR groups did not significantly differ in terms of R0 resection rates [83.8% vs 65.5 %, respectively; OR = 1.65; 95%CI: 0.29-9.30;  $P =$  not significant].

A systematic review and meta-analysis of four retrospective studies[136] enrolled 216 patients of Asian populations endoscopically treated for rectal carcinoids of size  $\geq 10$  mm. A non-significant difference of *en bloc* resection (90.6% vs 93.6%; OR = 0.82; 95%CI: 0.25-2.70;  $P = 0.74$ ) and R0 (79.4% and 78%; OR = 1.53; 95%CI: 0.62-3.73;  $P = 0.35$ ) between ESD and EMR methods was shown.

Another meta-analysis of seventeen heterogeneous retrospective Chinese studies [137], evaluating the endoscopic outcomes of 2003 sessile polyps ( $\geq 5$  mm) (mostly carcinoids), revealed a significantly higher *en bloc* resection rate (92.0% vs 89.8%, respectively; OR = 2.81; 95%CI: 1.39-5.70;  $P = 0.004$ ) using ESD than EMR as well as higher R0 rates (86.5% vs 61.4%, respectively; OR = 2.81; 95%CI: 1.39-5.70;  $P < 0.004$ ) for the ESD group.

Moreover, a meta-analysis of eight Japanese studies[103], including six cohort studies and two case-control series for a total of 1262 patients, compared endoscopic resection of sessile lesions of variable size and confirmed the highest percentages of *en bloc* resection (91.7% vs 46.7%; OR = 6.84; 95%CI: 3.30-14.18;  $P < 0.001$ ) and R0 resection (80.3% vs 42.3%; OR = 4.26; 95%CI: 3.77-6.57) using ESD than EMR.

A systematic review with meta-analysis[138] related to eleven retrospective studies (eight of them evaluating sessile polyps and three of any LST  $\geq 20$  mm) including 4678 Asian and French patients, displayed higher rates of *en bloc* resection (89.9% vs 34.9%; OR = 1.93; 95%CI: 1.46-2.54;  $P < 0.001$ ) and R0 resection (79.6% vs 36.2%; OR = 2.01; 95%CI: 1.76-2.29;  $P < 0.001$ ) for ESD than EMR.

Finally, in a systematic review of 66 Western and Asian studies[107] evaluating a total of 13659 sessile polyps/LST lesions, the percentage of *en bloc* resection was 90.5% after ESD and 62.8% following EMR (OR = 0.18; 95%CI: 0.16–0.2;  $P < 0.001$ ). Notably, the R0 curative rate was higher after EMR (92.0% vs 82.1%; OR = 2.5; 95%CI: 2.2–2.7;  $P < 0.001$ ).

**Tumor size:** The tumor size was larger in the ESD group as compared to EMR in the three meta-analyses of Chao *et al*[137] (mean size not specified, OR = 3.09; 95%CI: 1.54-4.63;  $P < 0.001$ ), Fujiya *et al*[103] (mean size was reported only for three studies, OR = 7.38; 95%CI: 6.42-8.34), and Arezzo *et al*[138] (33.7 mm vs 27.4 mm, OR = 7.36; 95%CI: 6.27-8.45;  $P < 0.001$ ). The size of lesions in the other three studies was similar for all groups[134-136].

**Adverse events:** The perforation rate was higher in the ESD group, whereas the delayed bleeding rate was similar to the EMR group in the four studies of Chao *et al* [137] (5.9% vs 1.5%; OR = 5.27; 95%CI: 2.75-10.08;  $P < 0.001$  and 3.7% vs 3.3%; OR = 1.34; 95%CI: 0.81-2.20;  $P = 0.25$ ), Fujiya *et al*[103] (8.5% vs 0%; OR = 4.96; 95%CI: 2.79-8.85 and 2.0% vs 3.5%; OR = 0.85; 95%CI: 0.45-1.60), Arezzo *et al*[138] (4.9% vs 0.9%; OR = 3.19; 95%CI: 2.14–4.77;  $P < 0.001$  and 1.9% vs 2.9%; OR = 0.68; 95%CI: 0.44–1.03;  $P = 0.070$ ), and De Ceglie *et al*[107] (4.8% vs 0.9%; OR = 0.19; 95%CI: 0.15–0.24;  $P < 0.001$  and 2.04% vs 2.27%; OR = 1.1; 95%CI: 0.9–1.4;  $P = 0.3$ ), respectively.

Moreover in the study of De Ceglie *et al*[107], there was no meaningful difference in bleeding risk for ESD and EMR procedures. Also, ESD showed similar rates of post-procedural bleeding (3.6% vs 8.0%) and perforation (0.7% vs 8.0%) than the EMR group according to Zhong *et al*[134] and similar overall complication rates as observed by Wang *et al*[136] (18.3% vs 10.3%; OR = 0.67; 95%CI: 0.26-1.69;  $P = 0.40$ ) and by Wang *et al*[135] (8.9% vs 5.8%).

**Recurrence:** ESD was associated with a lower recurrence rate than EMR in the six studies of Wang *et al*[135] (0.98% vs 12.70%; OR = 0.09; 95%CI: 0.04-0.19), Wang *et al* [136] (0.9% vs 6.4%; OR = 0.15; 95%CI: 0.03-0.87;  $P = 0.03$ , when using the fixed-effect model), Chao *et al*[137] (1.0% vs 9.9%; OR = 0.14; 95%CI: 0.06-0.30;  $P < 0.001$ ), Fujiya *et al*[103] (0.9% vs 12.2%; OR = 0.08; 95%CI: 0.04-0.17), Arezzo *et al*[138] (0.7% vs 12.7%;

**Table 2 Characteristics of the seven included systematic reviews and meta-analyses on the comparison between the outcomes for endoscopic mucosal resection and endoscopic submucosal dissection procedures**

Ref.	Study	Nations	N patients/lesions	Type of colorectal lesions	Lesion size	Procedural time <sup>1</sup>	En bloc resection <sup>1</sup>	R0 <sup>1</sup>	Perforation <sup>1</sup>	Bleeding <sup>1</sup>	Surgery <sup>1</sup>	Recurrence <sup>1</sup>
Zhong <i>et al</i> [134], 2013	Systematic review with meta-analysis of 4 retrospective studies	Japan, Korea, China	243 patients/245 lesions (EMR: 106; ESD: 139)	Sessile (carcinoids)	< 15 mm	19.1 ± 11.1 vs 8.1 ± 9.4	92% vs 100%	69.1% vs 87.7%	2.8% vs 0.7%	2.8% vs 3.6%	0.7% vs 0%	2.9% vs 0%
Wang <i>et al</i> [135], 2014	Meta-analysis of 6 studies (case-control)	Japan, Korea	893 patients/1642 lesions (EMR: 866; ESD: 776)	Sessile or flat	≥ 10 mm	Range, 29.0-29.4 vs 87.2-108.0 min	44.5% vs 87.9%	65.5% vs 83.8%	5.8% vs 8.9% (overall complications)		NA	12.70% vs 0.98%
Wang <i>et al</i> [136], 2016	Systematic review with meta-analysis of 4 retrospective studies	Brazil, Korea, Japan, China	216 patients/216 lesions (EMR: 109; ESD: 107)	Rectal carcinoids (lesion morphology not specified)	≥ 10 mm	(150.0 ± 66.3/116.0 ± 58.5 ± 3.6/63.0 ± 54.0/50.0 ± 589.2) vs (133.0 ± 94.8/84.0 ± 51.2/131.0 ± 100.0/78 ± 176.7) min	93.6% vs 90.6%	78% vs 79.4%	10.3% vs 18.3% (overall complications)		NA	6.4% vs 0.9%
Chao <i>et al</i> [137], 2016	Meta-analysis of 17 studies (retrospective)	China	2003 patients/2003 lesions (EMR: 1054; ESD: 949)	Sessile: carcinoids (11 studies) or carcinomas (5 studies); LST (1 study)	≥ 5 mm	Range, 15.0-65.9 vs 3.5-29.4 min	89.8% vs 92.0%	61.4% vs 86.5%	1.5% vs 5.9%	3.3% vs 3.7%	NA	9.9% vs 1.0%
Fujiya <i>et al</i> [103], 2015	Meta-analysis of 8 studies (non-randomized, 6 cohort and 2 case-control)	Japan	1262 patients (EMR: 634; ESD: 628)/1763 lesions (EMR: 949; ESD: 814)	Morphological features of lesions in 7 studies were <sup>2</sup> , in the EMR group: 0-I (269 cases) and 0-II (679 cases); in the ESD group: 0-I (125 cases) and 0-II (680 cases); 576 adenomas and 380 carcinomas	≥ 20 mm (5 studies), ≥ 10 mm (1 study), > 5 mm (1 study)	Range, 29.0-30.0 vs 65.9-108.0 min	46.7% vs 91.7%	42.3% vs 80.3%	0% vs 8.5%	3.5% vs 2.0%	5.8% vs 9.9%	12.2% vs 0.9%
Arezzo <i>et al</i> [138], 2016	Systematic review with	Japan, Korea, France	4678 patients/4678	Sessile (LST-NG and LST-G)	≥ 20 mm (except in 3	29.1 vs 66.5 min	34.9% vs 89.9%	36.2% vs 79.6%	0.9% vs 4.9%	2.9% vs 1.9%	3.0% vs 7.8%	12.7% vs 0.7%

	meta-analysis of 11 studies (10 retrospective and 1 case-control)		lesions (EMR: 3161; ESD: 1517)	were also included in 3 studies): adenomas, carcinomas in situ, invasive cancers or carcinoids									
De Ceglie <i>et al</i> [107], 2016	Systematic review of 66 studies (3 RCTs; 22 prospective and 41 retrospective)	Germany, Taiwan, France, Japan, Greece, Great Britain, Czech Republic, Malaysia, Australia, Italy, China, United States, Brazil, Korea, Portugal, Serbia	13659 patients (EMR: 8660; ESD: 4999)/17950 lesions (EMR: 11.873; ESD: 6077)	Sessile or LST	LST-NG $\geq$ 20 mm and for LST-G $\geq$ 30 mm or $\geq$ 40 mm	NA	62.8% vs 90.5%	92.0% vs 82.1%	0.9% vs 4.8%		2.3% vs 2.0%	NA	10.4% (3.0% in <i>en bloc</i> and 12% in piecemeal) vs 1.2%

<sup>1</sup>Endoscopic mucosal resection vs Endoscopic submucosal dissection.

<sup>2</sup>According to Paris classification. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LST: Laterally spreading tumor; NG: Non-granular type; G: Granular type; RCT: Randomized controlled trial; NA: Not available.

OR = 0.06; 95%CI: 0.03–0.11;  $P < 0.001$ ), and De Ceglie *et al*[107] (1.2% vs 10.4%; OR = 8.19; 95%CI: 6.2–10.9;  $P < 0.001$ ). Only one meta-analysis[134] showed a similar recurrence rate between ESD and EMR (0% vs 9%).

**Surgery rates:** The data for the surgical rate for any reason was available only in three studies[103,134,138].

In the meta-analysis of Zhong *et al*[134], one patient underwent surgery as rescue therapy for non-manageable recurrence after EMR and none in the ESD group (0.7% vs 0%,  $P =$  not significant).

In the meta-analysis of Fujiya *et al*[103], the most frequent indication for additional surgery was, for both ESD and EMR groups, non-curative reasons rather than perforation (9.9% vs 5.8%; OR = 2.16; 95%CI: 1.16–4.03;  $P < 0.001$ ). This resulted from the analysis of two studies.

In the study by Arezzo *et al*[138], the overall surgery requirement for complications was higher in the ESD group (7.8% vs 3.0%; OR = 2.40; 95%CI: 1.51–3.82;  $P < 0.001$ ). In detail, the rates of surgery for complications (OR = 7.21; 95%CI: 2.19–23.76;  $P < 0.001$ ), and surgery for non-curative reasons (OR = 1.55; 95%CI: 1.03–2.33;  $P < 0.034$ ) were 3.0% and 6.9%, respectively, in the ESD group and 0.4% and 4.1% in the EMR group.

## CONCLUSION

Conclusively, it is crucial to enhance the preoperative diagnostic workup because the prevailing technology concomitantly with operator skills is still exceedingly misleading, especially in deciding the most suitable endoscopic method for radical resection of non-pedunculated colorectal lesions at risk of underlying malignancy. Admittedly, the prevailing unsolved challenge concerns the requirement for a secure SMIC estimation method to properly stratify the chance of the post-procedural necessity for surgery following ESD and proficient in determining the at-risk subgroups of patients in whom ESD could obtain the most fitting approach.

Additionally, ESD necessitates being further improved considering the excessively time-consuming as well as the intraprocedural technical hindrances and related complications, even in expert hands.

Therefore, in this time frame, it is demanded a substantial ability to choose and perform EMR when it is proper and ESD only when obliged by the highly suspected endoscopic features of colorectal lesions.

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