**Evaluation and Long term outcomes of the different modalities used in colonic EMR**

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**Summary**

The use of Endoscopic mucosal resection (EMR) to remove colonic polyps is a technique used in western countries for at least the last two decades. Significant experience has been accumulated and the efficacy of the method has been recently evaluated in large meta-analysis. A number of variations to modify the technique, which includes knife assisted, cap assisted, ligation devices, and underwater EMR have been developed in an attempt to improve outcomes. However, to date there is limited data that compares, or shows superiority of any one such technique. This article will review the current evidence of the efficacy of each of these modified techniques.

**Keywords:** Endoscopic mucosal resection, colorectal polyps, endoscopic mucosal resection-precutting

**Introduction**

Endoscopic mucosal resection is a well-defined technique for removal of precancerous lesions. It involves submucosal injection of fluid underneath a lesion which lifts it away from the muscular layer,facilitates easier snaring of flat or sessile lesions, reduces the risk of thermal transmural trauma and identifies lesions with submucosal invasion or scaring which are probable non amenable to endoscopic removal (1).

Several studies and meta-analysis in the recent years have addressed the efficacy of endoscopic mucosal resection (EMR) in treating large polyps within the colorectum, by assessing the recurrence rate , the number of follow up endoscopic procedures needed to treat the residual lesion, the need for surgery after EMR and the complication rates (2) (3). The EMR recurrence rate has been reported as high as 45% (4) and there are many contributing factors which will be discussed in this article but a significant issue is that a piecemeal dissection is required of lesions greater than 20mm. In contrast, the technique of endoscopic mucosal dissection (ESD) for lesions provides en bloc specimens that facilitates accurate histopathogical assessment of submucosal invasion and has a significantly lower recurrence rate. However, the disadvantages of ESD over EMR include; it is less accessible, it is significantly more time consuming , it has higher complication rates, it is more expensive, and there is a long learning curve with prolonged training required even for highly skilled endoscopists to master the technique. .

EMR has been an established technique for the last 25 years and the literature has lately provided high quality meta-analysis and data from prospective studies on its efficacy. Over the period there have been modifications in the technique in an attempt to improve outcomes of the procedure. However, comparative studies in the various modified techniques are lacking. The article will review the variations and modified techniques of performing EMR, highlighting the differences and merits of each technique based upon the current available literature.

**Indications for Endoscopic Resection**

The recent Japanese guidelines have set indications for both EMR and ESD (table 1,2 ) and have highlighted the need for endoscopic assessment of the lesion prior to resection to identify carcinomas and to assess the submucosal (SM) invasion depth. (5). ESD is an absolute indication for IIc, IIa+IIc lesions larger than 2cm. Also it is indicated for Lateral Spreading Tumors- Non Granular type (LST-NG) larger than 2 cm which have approximately 30-56% multifocal submucosal invasion primary superficial (SM1) (6) (Fig 1).

These indications are led by the need of the above lesions to be removed en bloc due the increased risk to harbour submucosal invasion . The higher incidence of submucosal fibrosis or submucosal invasion in these lesions could make EMR fraught as it would lead to inadequate lifting of the lesion after the submucosal fluid injection (non lifting sign). (2) Additionally, piecemeal EMR may make difficult to evaluate precisely the invasion depth and the free margins for carcinomas with less than 1000µm submucosal invasion depth (pT1a). Accurate histopathological evaluation is essential in these cases, which carry a low metastatic risk (1.5-1-9% in the colon and 4.2-4.5% in the rectum) and only endoscopic resection can be adequate, to prevent unnecessary surgery (7).

In vast majority of cases referred for EMR (>90%) within the Western world submucosal invasion/malignancy is not an important factor and therefore EMR can be used safely as the preferred technique (8). Even for Lateral Spreading Tumors-Granular Type (LST–G) > 2cm piecemeal EMR is an acceptable technique by the eastern world provided that the largest nodule which may contain carcinoma will be removed en bloc and the rest of the lesion piecemeal (planned EMR) (5) (Fig2,3).

The assessment for submucosal invasion is carried out by ordinary observation looking for surface unevenness, presence of depression and fold convergence, by magnifying observation(pit pattern diagnosis) using dye spraying ( indigo carmine, crystal violet etc) and image-enhancement technology [Narrow band imaging(NBI), blue laser imaging( BLI)] to assess fine surface structures and microvessels. Deep depression, expansive appearance, submucosal tumor like- margin or defective extension predict deep SM invasion in 70-80% which indicates direct referral for surgery.

The accuracy rate of discrimination between adenoma and carcinoma is between 70-90% using pit pattern observation or NBI. If the V pit pattern is observed in a lesion with dye spraying and magnifying observation the diagnostic accuracy of deep submucosal invasion is 90% (5) .

**Long term outcomes of standard EMR**

*Recurrence rate*

The recurrence rate following EMR is between 15-45%. Large series, however, suggest the realistic value to be around 15-18% (9). The recurrence if seen at follow up endoscopy is 91% at 6 months and 98% at 12 months. Consequently, follow up protocols of lesions vary with first follow-up at 3 to 6 months and another at 12 months as studies have highlighted that recurrence can occur after an normal initial follow up endoscopy in up to 12% cases (3) (10).

The main predictors for recurrence have been shown to be piecemeal resection and increased polyp size. . Lesion size of greater than 20mm (unsurprising as piecemeal resection is required) has been shown to be significant (11). A study has shown if lesion is 40mm or more, there is a greater than 8 fold increase in the incidence of recurrence (9).

91.4-93% of the recurrences are successfully treated after a mean number of 1.2 endoscopic treatments with either APC or EMR (3) (9)).

There is conflicting evidence for the effect use of argon plasma coagulation (APC) on recurrence. The reason is that whilst some meta-analysis have not identified this is a significant factor, other studies have shown a greater than 2 fold effect. The issues include that many studies have not identified the use or non-use of APC within the procedure, the context, i.e. use when clearance could not be attained or in context of prophylaxis when clearance was achieved etc (12) (13) (14) (15). Prospective randomised trials are need in this area. Other factors that have been identified include proximity to colonic folds and intra-procedural bleeds.

Other modalities used to reduce the recurrence rate or to treat recurrent adenomas are the Endoscopic Mucosal Ablation (EMA) and the Hot Avulsion technique which are also rescue treatments for fibrotic recurrent adenomas

Endoscopic mucosal ablation (EMA) a novel technique for the eradication of recurrent polyps with extensive submucosal scarring , combines submucosal fluid injection with high power APC . The submucosal injection provides a safety cushion which protects the muscularis propria as high power APC needs to be applied for the eradication of extensively scarred residual polyps, In a pilot study , EMA, as a “rescue” treatment, successfully eradicated 82% of fibrotic recurrent polyps. (16)

Hot avulsion (HA), is a new variation of the Hot Biopsy(HB) to eradicate residual or recurrent fibrotic adenomatous tissue especially after snare polypectomy has failed . Hot biopsy forceps are used to grasp neoplastic tissue with slight traction away from the polyp base while current is applied. The main difference between HA and HB is that HB uses forced coagulation current which can result in transmural inury while in HA Endocut I or soft coagulation current is used. Studies have shown reduced recurrence rate when macroscopically visible residual adenoma, non amenable to snare resection, is treated with HA compared to APC ( 10% vs 59.3%) (17).It also very promising in eradicating fibrotic recurrent polyps with a success rate in small case series up to 100%. (18) (19)

**Complication rates**

The delayed bleeding rates have been reported to be 1.6%, 1.15%–1.7%, and 0.7%–2.2% for polypectomy, EMR, and ESD, respectively (20) (21). In low volume centres the delayed bleeding rates for large lesions have been reported up to 25% highlighting the need for tertiary referral.

In recent large studies the rate of clinically significant bleeding post EMR for lesions >20mm is 5-7% . (22) (23) (24) Risk factors for post EMR bleeding are lesions >30mm (OR 2.5), proximal colon location ( OR 2.3), any major comorbidity at procedure (OR 1.5), epinephrine injection in the EMR solution (OR 0.57) and the use of a non-microprocessor –controlled electrosurgical current. (25) . The use of aspirin during large EMRs has been evaluated in only two studies . An observational study with 302 lesions found an OR of 6.3 but a prospective multicentre study with 1,172 lesions found no significant association (23) (26)

55% of post EMR bleeding stops spontaneously while the rest will need endoscopic treatment and 1% will need primary embolization or surgery (28).

The prophylactic use of clips has been evaluating and although it seems to decrease the delayed bleeding rate, it is not cost effective (27). Probably an individualised approach in cases with high risk for delayed bleeding would be preferentialMoreover prophylactic endoscopic coagulation of the exposed vessels in the mucosal defect of EMR does not seem to prevent delayed bleeding. (29)

The perforation rates during endoscopic resection are reported to be 0.05%,

0.58–0.8%, and 2%–14% for polypectomy, EMR, and ESD, respectively (20).

In haemodynamically stable, nonimmunosuppressed patients with adequately prepared bowel and no signs of generalized peritonitis, application of endoscopic clips and antibiotic administration has been reported to favourably treat iatrogenic colonic perforations, with success rates ranging between 81.3% and 100% (30) (31)

Over-the-scope clipping devices have shown good results with up to 90% successful closure of perforations although larger studies are needed to fully assess the efficacy and safety of these devices. (32)

**Long-term curative rates & Surgical Intervention**

Overall surgical intervention is required after an attempted EMR in 8.3-13.5% of cases. This is due to (1) adverse histopathology i.e. invasive cancer following a successful EMR (3.7-4.8% of cases) (2) initial non curative resection for various reasons, as submucosal fibrosis, non-lifting sign and difficult positioning (2.3%-8.8%) or (3) complications encountered (0.5%) such as perforation or intractable bleeding (9) (2).

An important finding is that surgical referral for recurrences non amenable to endoscopic resection after initial successful EMR is needed only in 0.2%-1% of the cases (3).

**Modified EMR techniques**

***EMR- precutting (EMR-P)***

EMR-P is a technique that combines ESD tools with EMR to remove larger tumours which would be difficult to be snared en bloc with classic EMR. After the submucosal fluid injection the mucosa is incised 5-10mm away from the tumor with a flex knife. A 35mm oval snare is then applied round the tumor at mucosal incision site . The mucosal incision enables effective snaring without slippage of the snare.

A retrospectively study compared EMR, EMR -P and ESD for the treatment of large colorectal tumors (32) demonstrated that lesions removed by EMR and EMR-P were similar size, but EMR-P compared to EMR had significantly higher en bloc resection rates 65.2% vs 42.9% and complete resection rate 59.4% vs 32.9% respectively. The recurrence rate was 25% vs 3%. 90% of the recurrences of the EMR had piecemeal resection. All the recurrences but one who needed surgery in the EMR group were successfully treated with one additional EMR. Interestingly 15.7 % of EMR, 29% of EMR-P and 37.9% of ESD were adenocarcinomas . 9% of patients with adenocarcinoma treated with EMR underwent surgery due to uncertain margins in the histopathology vs 0% treated with EMR-P. In terms of complications perforation rates were not significantly different although slightly higher for EMR-P (2.9% compared to none in EMR group) .

EMR-P with additional submucosal dissection to a certain degree before snaring the lesion is the definition of hybrid/ simplified ESD or Knife-assisted EMR. The complication rate for the hybrid ESD seems to be similar to ESD and further studies are needed to set the indication of this procedure (33). In a recent prospective study (34) knife –assisted EMR was used to remove polyps unable to lift due to scar tissue .In the study ESD was performed for approximately 10mm round the polyp into the scar tissue before the lesion was snared. The success in polyp eradication was 90% ,with no perforations but there was a delayed bleeding rate of 5%.

Overall as it was highlighted the technique can be useful in cases where carcinoma is suspected and in the absence of ESD , en bloc resection is required to prevent unnecessary operation due to uncertain histopathogical margins. EMR-P seems to offer an intermediate method for endoscopist not experienced to ESD. In the correct hands , it has good technical success rates with the advantages of low recurrence rate and higher en bloc resection . Randomised controlled head to head studies are needed as it may carry higher complication rates than traditional EMR.

**Underwater EMR**

This novel EMR technique was described first described in 2012 ( (35) where polyps larger than 2cm were snared without prior submucosal injection. Instead, the lumen was initially deflated and the polyp was totally immersed with water using a water pump. The hypothesis for the technique was based on an observation made during colonic EUS where was noticed that when the lumen is filled with water the colonic muscular propria remains circular and the water floats the mucosa and submucosa away from the deeper muscular layer creating a safety cushion. Few single centre prospective studies has given good results (36). A recent study with the largest series of 81 polyps underwent underwater EMR demonstrated en-block resection in two thirds of the cases. Successful EMR with no macroscopic residual tissue was demonstrated in all cases. (37) and no recurrence was seen at 3 months follow up.

Another recent prospective study, with lesions between 2-4cm were removed en bloc with a 33 mm snare. The study design was based on the observations that water immersion results in less distension of the bowel lumen , contraction of the adenomatous tissue, and reduction of the haustral folds enabling the snare to capture larger mucosal surface even in lesions straddling a fold. In 55%, complete en bloc resections was achieved and no recurrence in these cases. In those that needed piecemeal resection the recurrence rate was 5% at 4- 6 months follow up . (38)

Almost 200 underwater EMRs have been preformed in few prospective studies up to date . Interestingly no perforation has been reported . The main complication reported is delayed bleeding at 0.5-5% with no need of transfusion or intervention. (39) The intraprocedural bleeding was rare and minor and usually ceased after flushing for 1 minute.[[1]](#endnote-1)

Disadvantages of the technique are the need of good bowel preparation and that the views are poor when there is vigorous bleeding.

Interestingly, the study confirms a previous study where the use of heated water at 37 degrees to fill the lumen reduces the bowel peristalsis (40)

The technique appears as a promising method of EMR due to significantly low adverse events reported , the reduction in procedure time, the possible cost effectiveness and the short learning curve (39) Also there is possibility that larger lesions can be removed en bloc leading to negligible recurrence rates. Large multi centre studies are needed to determine the efficacy and complications of the technique.

**Cap –assisted EMR (C-EMR)**

Cap-assisted EMR is a modified technique where a transparent plastic mucosectomy cap is mounted on the tip of the colonoscope. The cap has in his distal end a gutter that positions the opened polypectomy snare. The polyp is lifted with submucosal fluid injection and the cap is placed against the polyp. Mild suction is applied so the polyp to fill half of the cap . The snare is closed round the aspirated mucosa and the lesion is resected.

C-EMR has been used for EMRs in the upper GI Tract mainly the stomach and oesophagus but the use of this method in colon is not popular due to the possible entrapement of muscularis propria in the cap with consequent perforation

In the largest study to date 255 cases of C-EMRs performed in lesions larger than 2cm (41). The median diameter of the resected specimens was 13mm (range 12-16). All polyps were removed piecemeal. The median size of the LSTs were 30mm (range 20-100) and of the sessile polyps 25mm (20-80).APC was used for residual tissues in 22.3% of the cases.

The recurrence rate at a median period of 12.1 months ( 5.5-71.2)months was 4% and the recurrent polyps were treated endoscopically with APC or EMR in 1 session.

Intra-procedural bleeding occurred in 7.4% managed endoscopically. No delayed bleeding and no perforations occurred. Conio et al highlighted the need of controlled suction to prevent perforation and commented that in many cases suction is not necessary as pressure against the lesion causes its protrusion into the cap .

The advantages of C-EMR were confirmed in a recent retrospective study which included 124 polyps removed C-EMR. (42). In the study 60% of the lesions were larger than 2cm. The decision of C-EMR was made case by case as considered the best method for flat polyps in difficult locations. Of the polyps included, 45% were flat polyps , 14% were polyps involving the ICV, and 5% were polyps involving the appendiceal orifice.

The recurrence rate was 1.2% after a successful c EMR at median follow up 4.2 months ( range 1.6-46.8 months),while in all attempted c EMRs the successful polyp removal was 91 % . The rest failed due to inadequate grasp of polyp (scarring/carcinoma) and difficult position/size.

The perforation rate was 3.9% of which 2 cases needed surgery and the rest were managed endoscopically with endoclips. Perforations rates in previous studies with small number of patients were 2.5-4%. There was 3.9% intraprocedural bleeding and 2.4 % delayed bleeding managed endoscopically.

The cap seems to offer better visualisation of the operative field and the possibility to resect lesions located in difficult places. The cap is advantageous in interhaustral lesions and lesions involving the ileocecal valve (ICV) as increase the exposure of the lesion helping to keep the ileum distended and facilitating the placement of the snare..

Despite the fact that C-EMR is a technique for piecemeal EMR in all the above studies the recurrence rate is low, probably due to the improved visualisation of the field and the suction of normal mucosa along with the lesions at the margins of the lesion. The technique needs adequate training as it has increased perforation rates in none experienced hands. Most of the perforations occur in the first quarter of the period included in the study as the endoscopist gained experience.

**Endoscopic Mucosal resection with a ligation device (ESMR-L)**

This modified EMR has been used to remove small rectal neuroendocrine tumours . A multi band ligation device is mounted on the colonoscope. Submucosal saline solution is injected beneath the the tumor to reduce the risk of perforation. The lesion is then aspirated into the ligation device and an elastic band is deployed. The snared lesion is then resected below the band.

Carcinoid tumours less than 1 cm in the rectum have low risk of metastatic disease and local treatment is considered curative. As the carcinoids extends to the submucosa resection techniques used must aim for complete resection . The use of ligation device in the oesophagus has showed a maximum thickness of submucosa resected up to 1200µm (median 800µm range 500-1200) (43)

The efficacy of ESMR-L to resect small rectal carcinoids has been compared to standard EMR and ESD . Complete resection with negative histopathologically margins has been reported in 100- 94.3% of ESMR-L vs 80-75.7% of EMR cases (44) (45). ESMR-L compared to ESD has shown equivalent complete resection rates 92% (ESD) vs 100% for ESML- P with the advantage of ESML-P to be shorter in duration with shorter if any at all hospital admission (46).

No perforations occurred in all the above studies. The results of recent metanalysis confirm that treatment of rectal carcinoid tumors with ESD or ESMR-L is superior to EMR, and the efficacy of ESMR-L is equivalence to ESD treatment (47).

**Concluding Remarks**

Classic EMR, especially in tertiary centres can successfully remove more than 90% of the polyps. Any variation of the technique should aim to resolve specific problems where classic EMR is not successful as submucosal fibrosis, polyps in difficult locations ,or superficial submucosal invasion (SM1) . The variations discussed are promising but large studies are needed until they are widely adopted.

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Table 1. Indications for ESD for colorectal tumours (Japanese guidelines)

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| Lesions for which endoscopic en bloc resection is required   1. Lesions for which en bloc resection with block EMR is difficult to apply  * LST-NG * Lesions showing a V1-type pit pattern * Carcinomas with shallow T1 (SM) invasion * Large depressed -type tumours * Large protruded –type lesions suspected to be carcinoma |
| 1. Mucosal tumours with submucosal fibrosis |
| 1. Sporadic localised tumours in conditions of chronic inflammation such as ulcerative colitis 2. Local residual or recurrent early carcinomas after endoscopic resection |
|  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 2 Indications for colorectal ESD and EMR at National Cancer Centre Hospital in Japan** | | | | |
| Non invasive patterns should be diagnosed by chromo magnification colonoscopy | | | | |
| Tumor size (mm) | <10 | 10-20 | 20-30 | >30 |
| 0-IIa, IIc,IIa+IIc(LST-NG) | EMR | EMR | ESD candidate | ESD candidate |
| 0-Is+IIa (LST-G) | EMR | EMR | EMR | Possible ESD candidate |
| 0-Is (villous) | EMR | EMR | EMR | Possible ESD candidate |
| Intramucosal tumour with non-lifting sign | EMR | EMR/ESD | Possible ESD candidate | Possible ESD candidate |
| Rectal carcinoid tumour | ESMR-L | ESD/Surgery | Surgery | Surgery |

Fig 1. Case 1: EMR of LST-NG in the transverse colon

Fig 2. Case 2 :EMR of LST-G

Fig.3 Case 3: EMR of LST-G

1. [↑](#endnote-ref-1)