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Colorectal endoscopic mucosal resection (EMR)

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Colon polyps
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Outcome

A B S T R A C T

Colonoscopy has the benefit of detecting and treating precancerous adenomatous polyps and thus reduces mortality associated with CRC. Screening colonoscopy is the keystone for prevention of colorectal cancer. Over the last 20 years there has been increased in the management of large colorectal polyps from surgery to endoscopic removal techniques which is less invasive. Traditionally surgical resection was the treatment of choice for many years for larger polyps but colectomy poses significant morbidity of 14–46% and mortality of up to 7%. There are several advantages of endoscopic resection technique over surgery; it is less invasive, less expensive, has rapid recovery, and preserves the normal gut functions. In addition patient satisfaction and efficacy of EMR is higher with minor complications. Thus, this has facilitated the development of advanced resection technique for the treatment of large colorectal polyps called as endoscopic mucosal resection (EMR).

Background

Cancer-related death by colorectal cancer is the second leading cause in men and the third leading cause in women worldwide [1]. It is expected to cause about 50,260 deaths during 2016 [1]. The lifetime risk of having CRC is about 4.7% (about 1 in 21) for men and 4.4% (about 1 in 23 in women). However, the death rate from colorectal cancer has been decreasing both in men and women for several decades. Several factors contributed this decreasing trend; like screening colonoscopy for average-high risk individuals, through examination of colon and rectum and removal of polyps at the time of examination [2–4]. An increase in adenoma detection rate is one of the quality markers of colonoscopy which is associated with complete polyp resection thus breaks the adenoma-carcinoma sequence of polyps which in time leads to cancer [5]. The majority (90%) of colorectal polyps found in colon are diminutive polyps and are less than 1 cm [6]. These polyps are routinely managed by the gastroenterologists as resection does not pose considerable technical difficulty. However, some polyps (10–15%) are considered difficult; like size larger than 2 cm, located at two haustral folds or in certain regions in colon (involving ileocecal valve or close to the dentate line) [7]. These lesions and polyps >20 mm are managed with EMR.

The basic principle of EMR is expansion of submucosal space to create a plane for safe resection of colorectal polyps without injuring muscle. The history of EMR technique goes back to 1955 when injection was first used by Rosenberg to create a plane for fulguration of sigmoid and rectal polyps [8]. Later in 1973 Deyhle [9] used submucosal injection to the flat or sessile lesions to facilitate complete removal. But the technique was popularized among Japanese physicians only in the 1990s [10]. Now endoscopic mucosal resection for large $\geq$2 cm, flat or laterally spreading tumors has become a standard of practice for management of large colorectal polyps throughout the world [11–13]. Improvement in EMR technique is evolving every year. Other methods, such as ESD for *en-bloc* and curative resections are important for lesions predicted to have superficial submucosal cancer. ESD is discussed in detail elsewhere in this book. Currently, piecemeal EMR remains the standard management of most large colorectal polyps in Western countries where as ESD is primarily used in Asia. In this review we discuss lesion selection, available techniques, adverse events and outcomes, and suggest potential future improvements in EMR of colorectal polyps.

Lesion assessment

Selection of lesions is one of the important factors to be considered before EMR so as to avoid the resection of deeply

Abbreviations: EMR, Endoscopic mucosal resection; CRC, Colorectal cancer; LST, Lateral spreading tumor; VS, Viscous solution.

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invasive lesions which is non-curative and may have higher risk of perforation [14,15]. Polyps >2 cm and lateral spreading lesions (LSLs) are usually discovered by the community gastroenterologists who may refer patients to experts at high volume tertiary center for colonic EMR. Endoscopic prediction of dysplasia and invasive carcinoma for larger polyp is difficult, but this endoscopic skill helps in real time in choosing the appropriate resection technique. Ideally all the lesions should be classified morphologically on the basis of Paris classification in addition to surface topography (granular or non-granular) [16,17]. This is helpful is stratifying the risk of submucosal invasion [12,18]. Based on Paris classification, polyps with superficial appearance (category 0) are differentiated in: polypoid type (lesions 2.5 mm above the mucosal layer: pedunculated (0-1p), sessile (0-1s), or mixed (0-1sp)), non-polypoid (lesions less than 2.5 mm (0-11a), flat (0-11b)) or slightly depressed (0-11c) and mixed types [19] (Fig. 1). The cut-off length of 2.5 mm is a random measurement which usually relates to the length of biopsy forceps when closed. This threshold of 2.5 mm is not consistent as many sessile lesions are not uniform in their surface pattern. The risk of invasion proportionately increases with lesion size and the degree of depression. For example, Paris 0-1 $\leq$5 mm lesions have essentially 0% risk of harboring invasive cancer to 90% for 0-3c $\geq$15 mm lesions. In general Paris 0-2B and 0-2C carry higher risk of colorectal invasion and high grade dysplasia [20]. Depressed lesions with ulcerations or gross wall deformity have a high probability of harboring deeply invasive cancer and should be biopsied with tattoos placed on the anal side of the lesion to aid recognition of the lesions for later surgical resection [21,22].

Lateral spreading tumors are split into the granular (LST-G) and non-granular type (LST-NG) [23]. Non-granular lateral spreading lesions are subtle in appearances which can be easily missed by the endoscopists. The incidence of LST on routine colonoscopy is approximately 9% [24]. Granular type LST lesions are composed of nodules forming a flat broad-based area which this features are absent in non-granular LST lesions [25]. LST-Gs smooth surface have lower risk of local invasion (<2%) compared to LST-Gs with mixed-size nodules (7% for <20 mm and 38% for >30 mm) [14]. The risk of invasion further increases for LST-NGs type having thinner center (also called as pseudo-depression): 12.5% for <20 mm and 83% for >30 mm [23]. Although depressed lesions are rare (1–6%), the overall risk of local invasion is highest (27–36%).

Visual assessment of lesions can be increased with an addition of advance imaging technologies like FICE scan (flexible spectral imaging color enhancement), Narrow Band Imaging (NBI), use of topical dye (methylene blue or indigo carmine), i-SCAN (image enhanced endoscopy) or blue laser/light imaging (BLI). Blue light imaging technologies focus on the microvascular structures whereas imaging using dye helps to demonstrate crypts or pit openings. Based on chromoendoscopy surface pattern of polyp is classified according to the Kudo classification [26] Fig. 2. Precise assessment of vascular patterns according to the Sano classification or more recently used NICE criteria (Narrow-Band imaging International Colorectal Endoscopic criteria) and JNET (Japan NBI expert team) is important Figs. 3 and 4 [27–29]. Conventional adenomas like tubular adenoma are typically large with organized brown capillary network surrounding pits (Sano/NICE type 2) or elongated pits (Kudo type 3). Suspicion of invasive cancer is high with Kudo type 5 (when absent pits are present or irregularly mixed types or nonstructural present), or Sano/NICE/JNET type 3 (when irregular complex branching capillaries or avascular areas are seen). Kudo type 1 and 2 pit patterns lesions are non-neoplastic where type 3 and 4 lesions are more likely to harbor low grade dysplasia [30]. Unfortunately, current systems, even the most recent JNET classification, fail to accurately distinguish non-invasive/minimally invasive lesions that can be resected by piecemeal EMR, from superficially invasive lesions which benefit from ESD [29]. Lifting of lesions is a common practice of some experts to make sure that it is amenable to resection if the lesion lifts or if not adequate lifting referred for surgical resection. A downside of this technique is that sometime previously biopsied or incomplete resected lesions do not lift due to extensive fibrosis and submucosal trussing of the lesions [31,32]. However, complete endoscopic resection with complex EMR (EMR with hot avulsion and thermal ablation) is still preferable to surgical resection [33,34].

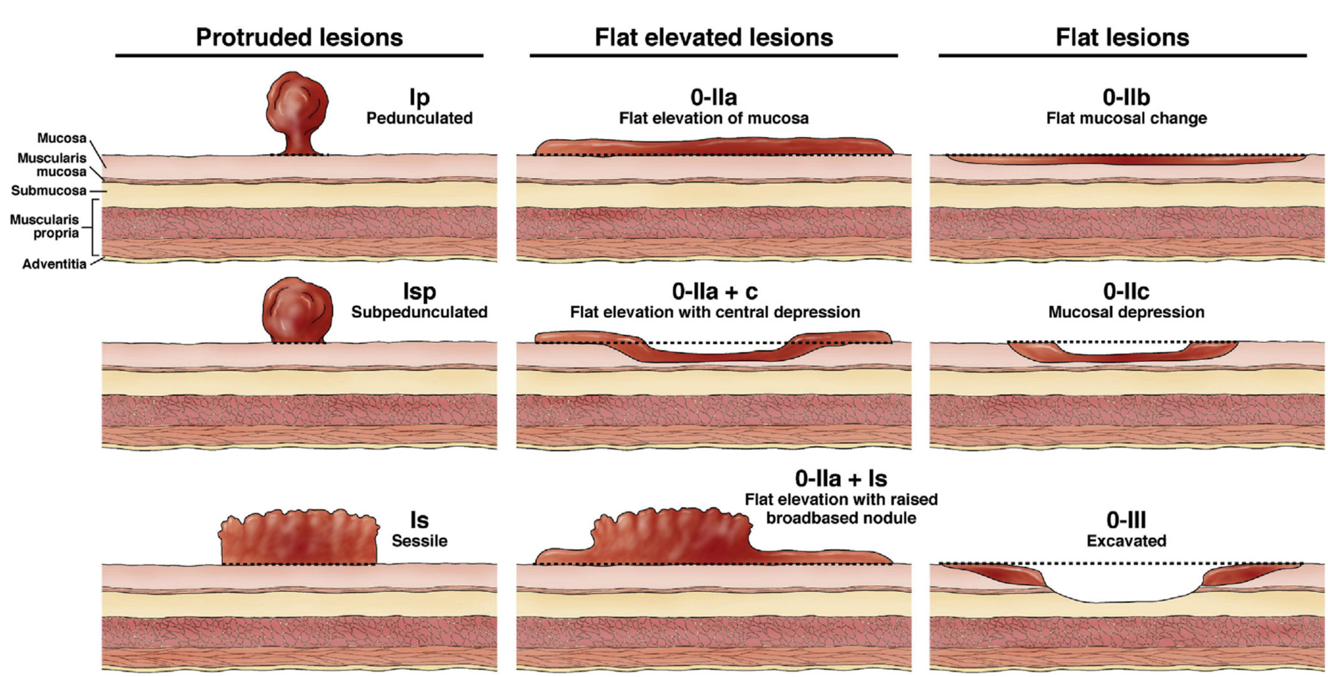
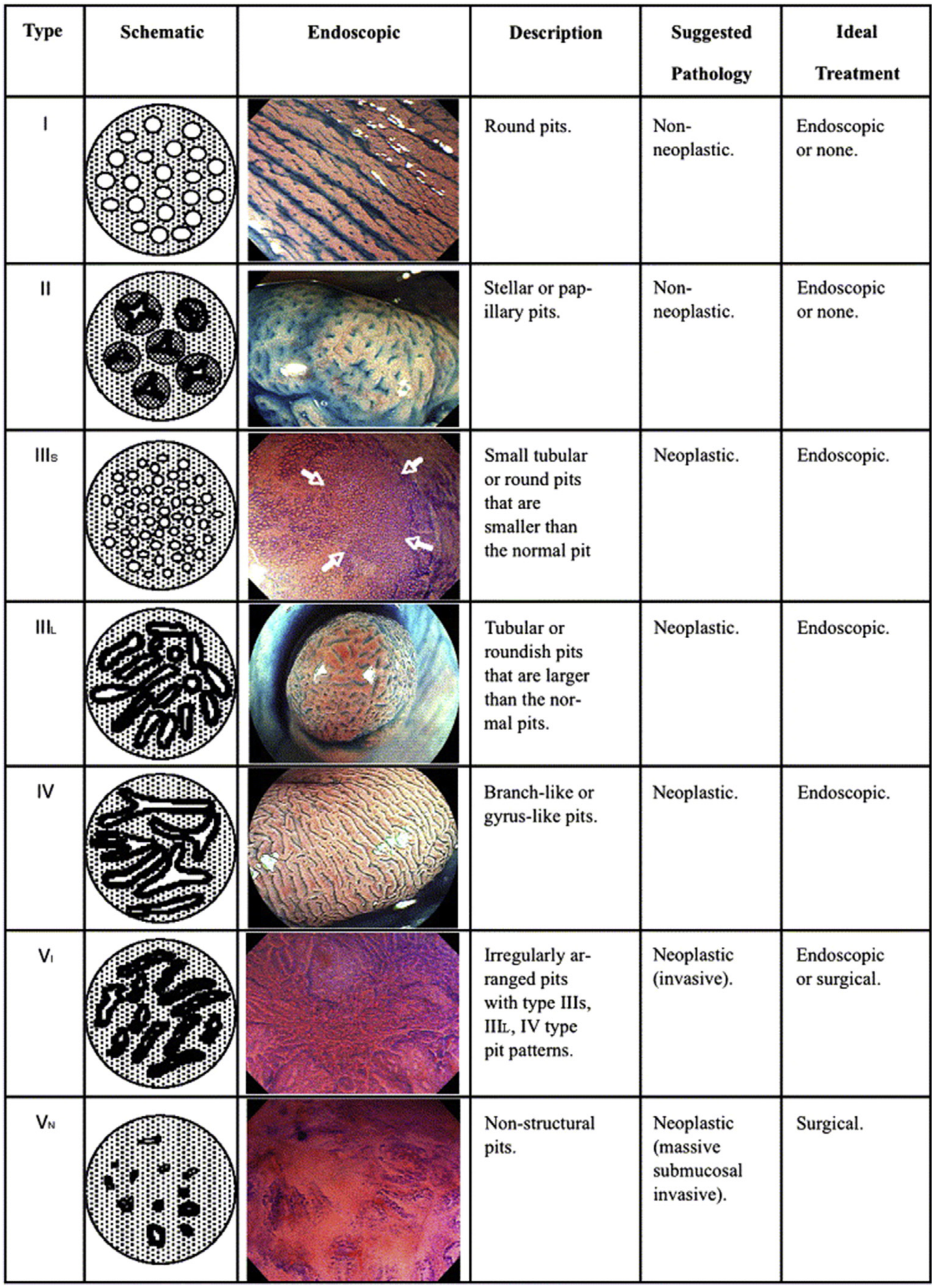


Fig. 1. Adapted from Holt and colleagues (Holt et al., 2012, Clinical Gastroenterology and Hepatology. 2012; 10 (9): 969–979) with permission from Elsevier.



Type	Schematic	Endoscopic	Description	Suggested Pathology	Ideal Treatment
I			Round pits.	Non-neoplastic.	Endoscopic or none.
II			Stellar or papillary pits.	Non-neoplastic.	Endoscopic or none.
$\mathrm{III_S}$			Small tubular or round pits that are smaller than the normal pit	Neoplastic.	Endoscopic.
$\mathrm{III_L}$			Tubular or roundish pits that are larger than the normal pits.	Neoplastic.	Endoscopic.
IV			Branch-like or gyrus-like pits.	Neoplastic.	Endoscopic.
$\mathrm{V_I}$			Irregularly arranged pits with type IIIs, $\mathrm{III_L}$, IV type pit patterns.	Neoplastic (invasive).	Endoscopic or surgical.
$\mathrm{V_N}$			Non-structural pits.	Neoplastic (massive submucosal invasive).	Surgical.

Fig. 2. Adapted from Tanaka and colleagues (Tanaka et al., 2006, Gastrointestinal Endoscopy. 2006; 64 (4): 604–613) with permission from Elsevier.

EMR technique

Pre-procedural preparation

Insufflation of gas is necessary to allow distension of the lumen in order to evaluate the mucosa. Insufflation with CO_2 is recommended based on the findings of a recent systematic review and a prospective cohort study, in which the use of CO_2 insufflation during EMR of large colonic lesions was associated with reduced post procedural admissions for pain, flatus and bowel distention, as compared with insufflation of air [35,36].

Lesion should be positioned at 5 to 6 o'clock in the endoscopic field before EMR, opposite of biopsy channel, in which patient is positioned in a way that any fluid or resected specimens accumulate away from the lesion [37,38]. The lesion should then be cleaned to allow adequate visualization [4].

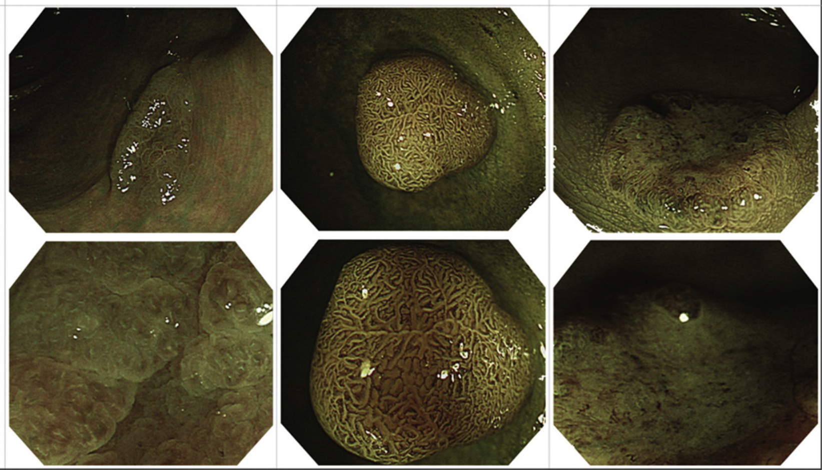
Among all the techniques described up to date, the conventional inject and cut technique has been the most widely used in the colon. It is comprised of submucosal injection, snare resection, evaluation of the mucosal defect, and removal of adenoma islands, if needed [39].

Submucosal injection

Submucosal lifting of the lesion with an injection away from the submucosal vessels facilitate better snare capture. It enables

NBI International Colorectal Endoscopic (NICE) Classification*

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structures**	Has area(s) of disrupted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structure surrounded by brown vessels**	Amorphous or absent surface pattern
Most likely pathology	**Hyperplastic**	**Adenoma*** **	**Deep submucosal invasive cancer**
Examples			



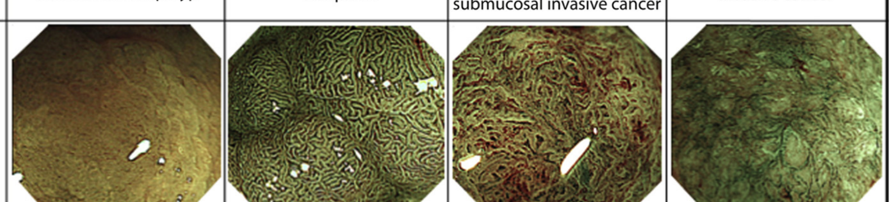
* Can be applied using colonoscopes with or without optical (zoom) magnification
** These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.
*** Type 2 consists of Vienna classification types 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

Fig. 3. Adapted from Hayashi and colleagues (Hayashi et al., 2013, Gastrointestinal Endoscopy. 2013; 78 (4): 6) with permission from Elsevier.

safe complete resection, while preventing perforation and deep thermal injury [40,41]. Submucosal injection fluid is comprised of 3 elements: viscous or normal saline solution, diluted epinephrine, and an inert dye. Viscous or normal saline provides a submucosal cushion, promoting a safe and complete resection. Diluted epinephrine may be used to reduce intra-procedural

Japanese NBI Expert Team (JNET) classification

NBI	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	• Invisible *1	• Regular caliber • Regular distribution *2 (meshed/spiral pattern)	• Variable caliber • Irregular distribution	• Loose vessel areas • Interruption of thick vessels
Surface pattern	• Regular dark or white spots • Similar to surrounding normal mucosa	• Regular (tubular/branched/papillary)	• Irregular or obscure	• Amorphous areas
Most likely histology	Hyperplastic polyp/ Sessile serrated polyp	Low-grade intramucosal *4 neoplasia	High-grade intramucosal *5 neoplasia/ Superficial *3 submucosal invasive cancer	Deep submucosal invasive cancer
Examples				



* 1. If visible, the caliber in the lesion is similar to surrounding normal mucosa.
* 2. Microvessels are often distributed in a punctate pattern and well-ordered reticular or spiral vessels may not be observed in depressed lesions.
* 3. Deep submucosal invasive cancer may be included.
* 4. Low-grade intramucosal neoplasia: low-grade dysplasia.
* 5. High-grade intramucosal neoplasia: high-grade dysplasia.

Fig. 4. Adapted from Sumimoto and colleagues (Sumimoto et al., 2017, Gastrointestinal Endoscopy. 2017; (http://dx.doi.org/10.1016/j.gie.2017.02.018) with permission from Elsevier.

bleeding. The inner dye (80 mg of indigo carmine or 20 mg of methylene blue in a 500-mL solution) facilitates delineation of the lesion margins, and allows confirmation of correct plane of resection [42].

Selection of the optimal solution to achieve submucosal cushion is crucial. Normal saline (NS) has been the most commonly used fluid to achieve submucosal lifting in EMR [41]. However, it is limited by its rapid tissue absorption that results in quick flattening. In order to overcome this limitation, the use of viscous, hypertonic solutions was implemented. Hydroxyethyl starch has proven to be an inexpensive solution that maintains submucosal elevation for a longer time than NS [40]. Sodium hyaluronate has proven to make EMR snaring process easier due to its high viscosity, with the disadvantage of requiring a large caliber needle and being more expensive [41]. Recently published a systematic review and meta-analysis by Yandrapu et al. compared the efficacy and complications of EMR using NS versus viscous solutions (VS) [43]. In lesions <2 cm, no significant difference was noted in en block resection between the NS and VS groups (OR, 1.21; 95% 95 CI, 0.32–4.60; $I^2 = 0\%$, $p = 0.78$). En-bloc resection had significantly higher odds in the VS group (OR, 2.09; 95% CI, 1.15–3.80; $I^2 = 0\%$; $p = 0.02$) for lesions >2 cm. Lower odds of residual lesions were noted in the VS group versus the NS group (OR, 0.54; 95% CI, 0.32–0.91; $I^2 = 0\%$). On subgroup analysis, there was no statistical difference among the VS and NS group for lesions >2 cm (9.25% vs. 13.46; $p = 0.3$). No significant difference in adverse events (post-polypectomy bleeding and perforation) was found between both groups (OR, 0.90; 95% CI, 0.48–1.70; $I^2 = 0\%$; $p = 0.75$). According to these results, VS should be considered for resection of colorectal polyps larger than 2 cm and NS for smaller polyps [43]. Most recently, there is a commercially available; FDA approved viscous solution for EMR/ESD that has been shown in preliminary studies to provide durable lifting (Rex et al. GIE 2017, 85(4), AB101; personal communication from the authors, Eleview, Aries Pharmaceuticals, San Diego CA, USA).

It is recommended to place a needle tip at tangential position, while slightly touching the mucosal surface. First, injection is performed by the assistant, and then followed by piercing the mucosa with the tip of needle. The injection catheter should then be pulled back while slowly deflecting the colonoscope up while maintaining the position of needle tip up in the submucosal plane [42]. Experts recommend 1 to 3 resections per injection [42]. There are several signs of inadequate injection: ongoing injection without tissue elevation, mucosal injection as demonstrated by immediate appearance of a superficial blue bleb without lifting of the lesion, a gush of fluid escaping the lesion at high pressure during injection, and canyoning non-lifting lesion with elevation of the perimeter of the lesion, with anchoring of the lesion in its original position. Poor lifting can be the result of submucosal invasion or fibrosis induced by prior attempts of resection or biopsy sampling [42].

Snare resection

There are multiple snares available. Selection of a specific snare depends on lesion size, morphology, location, or personal preference. Stiff wire snares are preferred to increase tissue capture. The 20–30 mm spiral snare may be used for large en bloc or wide-field piecemeal resections. Small thin wire snares (wire diameter, 0.3 mm) are used to remove tissue in difficult situations, such as submucosal fibrosis, periappendiceal, or residual adenomatous lesions at the margin of the defect [42]. Larger snares (20–25 mm) can be safely used in the rectum, while small (10–15 mm) might be used for lesions in the right colon [38].

Ideally, lesions are positioned at an orientation of 6 o'clock position. Resection of Is lesions should be attempted first in one piece and sent separately because these are more likely to harbor neoplasia [12]. A normal mucosa margin of 2- to 3-mm should be included. The edge of the defect should be used as the base for the next snare placement. The snare should be aligned along the defect margin to reduce the risk of adenoma islands. En bloc resection should be considered in lesions <20 mm. For large en bloc resections, snare longitudinal axis should be aligned with the lesion longest axis to optimize capture of tissue. To maximize tissue capture, the snare should be opened entirely covering the lesion, angled down resolutely with an up-down control onto the submucosal cushion while suctioning air. The snare should then be gradually closed while advancing the catheter to maintain the snare base at the lesion edge. The snare should then be closed tightly to exclude muscularis propria. Since sensory feedback is an unsatisfactory proxy of inefficient excision, three maneuvers have been described to assess safe tissue capture: 1) mobility: free mobility of snare catheter relative to the colonic wall upon back and forth movement of the snare catheter; 2) degree of closure: The snare should close nearly fully. The snare can be partly opened and tented into the lumen to free the deep-seated layers before repeated closure, if in doubt; 3) transection speed: While keeping the snare firmly locked, the foot pedal is pushed in short pulses. Transection should be fast. If not, muscularis propria entrapment or deeper invasion should be suspected [42].

Although there are no specific recommendations regarding the selection of the electro current settings, Bourke et al. suggest fractionated current alternating cutting and coagulating cycles (ENDO CUT mode Q, effect 3, cut duration 1, cut interval 6; ERBE, Tubingen, Germany) [42]. Prolonged coagulation current with an alternating cycles of high-frequency short-pulse delivered by microprocessor-controlled electrosurgical generators are commonly used. (VIO 300D; ERBE, Tubingen, Germany. ESG100; Olympus Medical, Tokyo, Japan) [42].

Removal of adenoma islands

It is best to avoid leaving isolated islands by careful placement of the snare at the edge of the last resection, ensuring a contiguous resection plan.

When complete island-free removal of a polyp with snare resection is not possible, multiple techniques have been described to manage residual tissue. Whenever possible, resective methods (avulsion, use of small-wire stiff snare) are preferred to ablative methods. Argon plasma coagulation has been described as an ablative treatment of residual islands of adenomatous tissue (forced coagulation, 40–60 W, .8–1.0 L/min, VIO 300 D; Erbe, Marietta, GA) [44]. Avulsion was recently described by Andrawes et al. to achieve complete removal of adenomatous tissue that cannot be lifted or entrapped in a snare due to fibrosis or submucosal invasion. It can also be used to remove polyps in difficult anatomical locations such as the ileocecal valve, the appendiceal orifice, and the angulations of the colon. The technique utilize hot biopsy forceps (Radial Jaw 4; Boston Scientific, Marlborough, Mass) which is conjoined with mechanical traction in combination with cutting current to cleave the remaining tissue [45].

A retrospective study by Holmes et al. compared the use of argon plasma coagulation vs avulsion for the treatment of residual neoplasia during EMR of non-pedunculated colorectal lesions >2 cm. Adenoma recurrence was defined as adenoma or cancer found at the resection site on the first EMR follow-up. Results showed that avulsion superior to APC for treatment of visible residual neoplasia during colorectal EMR (OR, 0.79; $p < 0.001$). Recurrence rate with APC: 53.9%, recurrence rate with avulsion: 10.3%. No significant difference in the adverse event rate was found between the APC vs avulsion groups [46].

Tsiamoulos et al. and colleagues have recently described a technique called "ablation and cold avulsion" of non-lifting and fibrotic lesions for the achievement of complete resection. The technique consists of ablation of residual tissue with high power APC (ERBE-VIO, 25–40 W, 1.6–2 L/min; Erbe, Tübingen, Germany), followed by removal of the remaining burned polyp with biopsy forceps. 2/14 patients had residual polyp on follow-up (3–7 months) [47]. The location of polyps >20 mm or those suspicious of invasive cancer should be tattooed with an India ink distal to the mucosal defect for subsequent scar examination on EMR-follow up [38]. The ink should not be placed into the polypectomy defect in order to avoid ink-induced fibrosis, which would hinder resection of recurrent lesions [31].

Modified EMR techniques

CAP-assisted EMR

Inoue described Cap-assisted endoscopic mucosal resection (C-EMR) first time for the esophageal lesions in 1990 [48]. In 1993, it was incorporated for removal of colorectal lesions [49]. The procedure consists of injection of fluid in submucosal space with solution of choice. Tip of the endoscope was attached a transparent hard straight plastic cap. Cap should be placed on the proximal border of the lesion. Light suction is then applied. The snare is closed once adequate tissue is suctioned into the cap. Suction is released and cautery is applied while closing the snare. Along these lines, Kashani et al. recently described a retrospective data to evaluate the safety and efficacy of C-EMR for non-pedunculated colorectal lesions (n = 124) [50]. The eradication rate for the polyps with available follow-up was 91% (81/89), whereas the overall complications rate was 10.2%. To date, there are no randomized trials comparing the inject-and-cut technique with C-EMR. Given the complications profile, and the high eradication rate reported by Kashani et al., C-EMR can be considered in high-experienced centers for flat lesions when standard EMR cannot be attempted [50].

Underwater EMR

Underwater EMR (U-EMR) is a modification of the conventional inject-and-cut technique that abolishes the need of injection on submucosal space. It was proposed by Binmoeller et al. as a salvage method to overcome residual fibrosis of adenoma recurrence after piece meal EMR of a LST [51]. It is based on the concept that after water immersion, muscularis propria of colon remains circular and not go along with involutions of the folds; therefore, a resilience effect is achieved on adenoma-bearing mucosa, with elevation of the lesion away from the deeper muscularis propria [51]. Air is evacuated from the affected segment of lumen, followed by infusion of water until complete filling is achieved. Narrow band imaging (NBI) is used to identify the adenoma margins, which are subsequently stained diathermically with APC coagulation (0.8 flows, 30 W). Snare resection with a stiff braided snare begins at polyp margins, followed by opening and positioning of snare to include normal mucosa margins marked with the diathermic dots. The open snare is pressed against the bowel wall and torqued to involve enough tissue followed by electrosurgical resection. The advantages of this technique include reduced time and cost, a very low rate of complications, and a lower recurrence rate as compared to conventional EMR (Table 1) [51–54]. Furthermore, Curcio et al. recently demonstrated that U-EMR could be safely performed by endospists skilled in EMR, with no prior training in U-EMR [52]. Regarding limitations of the technique, visibility can be compromised by intestinal peristalsis, and by poor colon preparation. Binmoeller et al. have used sterile water heated to 37 °C to overcome this drawback since 2015 [54].

U-EMR was initially intended for piecemeal removal of fibrotic lesions. However, based on the observation that there is contraction of the lesions after water immersion, Binmoeller et al. proposed a new technique to achieve en bloc resection of LST between 20 and 40 mm using a single large snare. Unfortunately, it only accomplished en bloc removal in 55% of lesions [54]. In a study published by Kim et al. compared the en bloc resection rate and the endoscopic complete removal of U-EMR with conventional EMR for recurrent colon polyps. Both the results were significantly higher in the U-EMR group. Independent predictor of successful en bloc resection and endoscopic complete removal was U-EMR [53]. Thus, further prospective, randomized, multi-center studies are required comparing these modified techniques to standard EMR, in order to consider training and subsequent incorporation into regular practice.

Endoscopic mucosal resection of ileocecal valve (ICV) and anorectal junction

EMR of LST in certain anatomic locations like ileocecal valve (ICV), AO and anorectal junction are technically difficult and challenging. These lesions are often managed surgically because of the concerns related to its complexity, safety and efficacy. Access to endoscopy is often restricted, and visualization is poor. There are few studies that have evaluated the outcome and effectiveness of EMR on above selected lesions.

In one single center prospective observational study, outcomes of EMR involving ICV was evaluated. Patients with >20 mm lesions were included over the period of 5-year. Complete adenoma clearance was accomplished in 93.6% and surgery was prevented in 81.3%. Bleeding was observed in 6.4%. No perforation was observed [55]. ICV EMR failure was associated with Ileal infiltration and involvement of both ICV lips. Early recurrence was detected in 17.5% and late recurrence in 4.5%. Endoscopic management of recurrent adenoma was successful.

In one prospective observational study, EMR of anorectal junction was performed. 100% complete adenoma clearance was achieved. In 22% cases focal adenoma recurrence was seen on first SC1 but was successfully managed. No recurrence was found on long term follow up. No difference was in terms of procedural success, adenoma recurrence, and the rate of hospital admission between proximal rectum and anorectal junction (ARJ) [56]. Transanal endoscopic microsurgery is advocated for distal rectal lesions, but it is more expensive, longer hospital admission, and may be associated with incontinence. On the other hand larger rectal lesions >20 mm could be resected en-bloc by ESD with complete resection of deep and lateral margins. But its application is not widely adopted in western countries as it requires specialized skills.

Thus EMR technique can be used as a first line management of large colorectal lesions in IC valve and ARJ in the absence of invasive disease.

Outcomes and complications after endoscopic mucosal resection of large colorectal polyps

Outcome

Endoscopic resection is safe and effective technique compared to surgery. In one meta-analysis from 50 studies included 6442 patients and 6779 large polyps. Surgical resection after EMR was as the primary end point of the study. Technical success rate of EMR was 90.3% (95% CI 88.2% to 92.5%). Mortality was 0.08% (95% CI 0.01% to 0.15%). More than 90% of the cases were spared from

Table 1
Studies evaluating efficacy of colorectal underwater EMR.

Study	Study design	Patients	Procedures (UEMRs vs EMRs)[a]	Polyp size, mean/median (mm) (UEMRs vs EMRs)[a]	Adverse events rate	En-bloc resection rate (U-EMR vs EMR)[a]	Endoscopic Complete removal rate, n (%) (U-EMR vs EMR)[a]	Follow-up, median months (IQR) (U-EMR vs EMR)[a]	Recurrence rate at follow up (U-EMR vs EMR)[a]
Binmoeller et al., 2012 [51]	Prospective, observational. Single, tertiary-care referral center	60	62	34/40	Delayed bleeding: 3 (5%) Perforation: 0%	0%	62 (100)	3.8 (1.8–5.7)	1/54 (1.9%)
Kim et al., 2014 [53]	Retrospective, cross-sectional. Single, tertiary-care referral center	80 (36 vs 44)	80 (36 vs 44)	34.7 vs 34.8, P = 0.845	Bleeding: 0 (0%) vs 2 (4.5) P = 0.195 Perforation: 0%	47.2% vs 15.9%, P = 0.002	32 (88.9) vs 14 (31.8), P < 0.001	Mean ± SD: 5.79 ± 1.67 vs 5.21 ± 2.97	10% vs 39.4%, P = 0.02
Curcio et al., 2015 [52]	Prospective, observational. Single, tertiary- care referral center	72	81	18.7	No adverse events	55 (68%)	81 (100%)	12	No recurrence at 3-month follow-up
Binmoeller et al., 2015 [54]	Prospective, observational. Single, tertiary academic referral center	50	53	30 (20–40)	4% (1 abdominal pain, 1 delayed bleeding)	29 (55%)	53 (100)	7.7 (1.7–17.7)	2/43 (5%)

[a] If applicable.

having surgical resection with an acceptable risk of adverse events [57]. Thus, the risk of surgery due to adverse event after EMR was appeared to as low as 1%, indicating the EMR of large polyps has favorable risk/benefit ratio. A systematic review by Ceglie et al. included 66 observational studies (22 prospective and 41 retrospective) and 3 RCTs. One of the main end points of the study was to see the success rate of EMR on large colorectal polyps. PEMR success rate 92% and EMR-*enbloc* resection was achieved in 62.8% cases [58]. In a large multicenter prospective study by ACE group, (Australian academic endoscopy units) 479 patients with 514 lesions were included in a cohort. EMR was attempted in 467 patients (96.9%) and complete excision was achieved in 89.2% cases [12]. The success rate was 91% in treatment naïve lesions, but decreased to 74.5% for the previously attempted lesions because of the submucosal fibrosis. This is because the lesions are more likely failed to lift and likelihood of incomplete excision with snare alone. In addition data from large retrospective studies have demonstrated piecemeal EMR is highly effective and safe management of large sessile serrated polyps [59,60].

EMR complications

Perforation

Colonic perforation after EMR of LST occurs in 1–2% cases [12]. Most of the cases with small defects are managed with endoscopic clipping and subsequent conservative management [61]. The "target sign" (a rounded cuff of muscle tissue seen centrally on the resected specimen) verifies the absence in muscle layer, and should demand a close examination of the EMR base for the sign of a full thickness defect [62]. In one study which included 445 patients with LST or sessile polyps' ≥20 mm, ten patients with histologically confirmed MP resection were identified intra-procedurally as a "target sign". All patients with target sign (TS) were managed endoscopically and did not require surgical treatment [62]. Perforation is often considered as a radiological diagnosis [63]. Although CT and especially multidetector CT have a higher sensitivity, the findings of free intraperitoneal or subdiaphragmatic air is uncommon [64]. Endoscopic appearance of muscularis propria (MP) as a "white tail" following EMR is called as deep mural injury (DMI). Or the appearance of white unstained area within a blue submucosa is sign of unintended muscularis propria injury. Recently a classification called Sydney Classification of Deep Mural Injury (DMI) has been proposed based on 911 lesions treated by EMR in a large prospective Australian cohort study. It includes the full breath of injury, ranging from type 1 (exposure of uninjured MP) to type 5 (full thickness perforation with peritoneal contamination (Table 2) and Figs. 5 and 6 [65]. Stratification of injury helps in identification of lesions severity, guide in treatment and avoid the delayed perforation. In the original study, type 3–5 deep muscle injury (DMI) occurred in about 3% of the cases. DMI was significantly associated with en bloc resection, transverse location and HGD or submucosal invasive cancer [65]. The necessity of surgery and mortality is reduced if the injury is identified early and managed with endoscopic closure [66] (Figs. 7 and 8).

Management of deep muscle injury

DMI 1: Exposure of uninjured MP fibers, no prophylactic treatment is required.

DMI 2: The plane between submucosa and MP is often unidentifiable. If deep injury is suspected prophylactic clip closure is recommended even though "target sign" is not apparent. Ideally all the type 2 injuries should be clipped.

DMI 3, 4, 5: This type of muscle injury corresponds to true MP injury and should be closed promptly to avoid extension or extra

Table 2
Sydney classification of deep mural injury following endoscopic mucosal resection EMR, endoscopic mucosal resection; MP, muscularis propria.

Classification	Explanation to the type of injury
Type 0	Normal defect. Blue mat appearance of obliquely oriented intersecting submucosal connective tissue fibers
Type 1	MP visible, but no mechanical injury
Type 2	Focal loss of the submucosal plane raising concern for MP injury or rendering the MP defect uninterpretable
Type 3	MP injured, specimen target or defect target identified
Type 4	Actual hole within a white cautery ring, no observed contamination
Type 5	Actual hole within a white cautery ring, observed contamination

luminal contamination. In about 0.5% cases there is an intraprocedural perforation and clinical significant perforation occur in 0.2%. Over-the-scope clip is often used to close this type of injury. But the major disadvantage of this device is that the scope has to be withdrawn to load the clip at the scope tip, and followed by the reinsertion of the scope before deployment. This delay in perforation closure increased the risk of bacterial contamination [61].

All patients without any signs or symptoms of perforation following 1–3 DMI can be discharged at same day. About 10% of patients present with DMI during EMR. Type 1 and 2 DMI is associated with increasing lesion size, submucosal fibrosis, and transverse colon location where as type 3–5 (target signs and perforations) are associated with en bloc resection, transverse colon location and HGD or SMIC [65].

Bleeding

Bleeding is one of the common complications after EMR, and can occur immediately after polyp removal or be delayed up to 3 weeks following the procedure [67]. About 7% of the patients do present with significant bleeding that requires hospitalization with further treatment like need of transfusion, repeat endoscopy with coagulation of vessels (STSC) or use of clipping [67]. Several factors contribute the bleeding risk like size of polyp; location of polyps, patient's coagulation status and resection technique either EMR or ESD.

Immediate bleeding

Wide-field EMR (WF-EMR) is an effective treatment of large colorectal polyps >20 mm [12]. This type of technique creates a large mucosal defect ranging from 30 mm to 100 mm and exposes submucosal vessels which increase the risk of intraprocedural bleeding (IPB). Bhain et al. has defined IPB as "Oozing or spurting of blood persisting for longer than 60 s and not responding to the water jet irrigation" [68]. IPB was reported in about 11.3% cases and bleeding was associated with increased in lesions size, Paris classification 0-2a + 1s, tubulovillous histology, and EMR endoscopists who performed <75 cases. Majority of bleeding was managed endoscopically. Results from a large prospective multicenter study

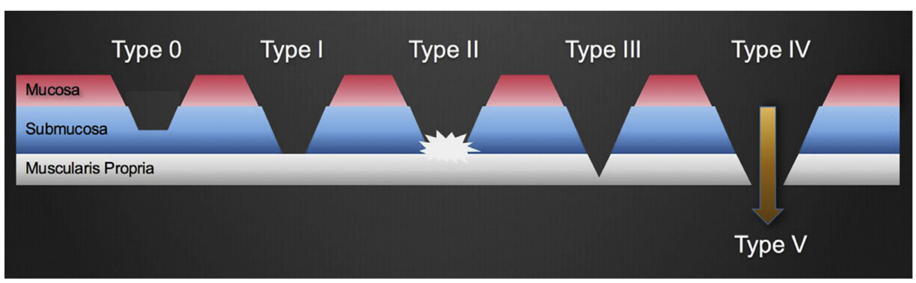


Fig. 5. Schematic of the Sydney classification of deep mural injury following endoscopic mucosal resection.
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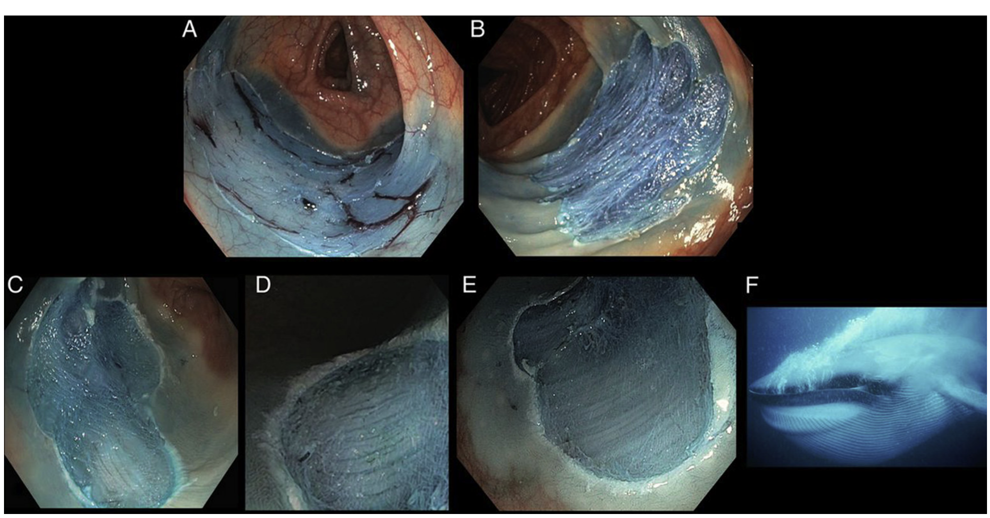

Fig. 6. (A, B) A **'type 0'** defect is a normal finding after resection. The mucosa has been completely resected revealing the underlying partially resected submucosa. The submucosa is homogeneously stained by the chromogelofusine dye. Submucosal vessels may be exposed but are uninjured. (C, D, E, F) A 'type I' defect occurs when the submucosa has been completely resected and the underlying muscularis propria (MP) is revealed. The MP does not avidly stain with the chromic dye so has a white appearance, and the circumferential striations of the muscle layer are seen. This appearance resembles the ventral pleats of a blue whale seen from underwater so is referred to as the 'whale' sign (F).
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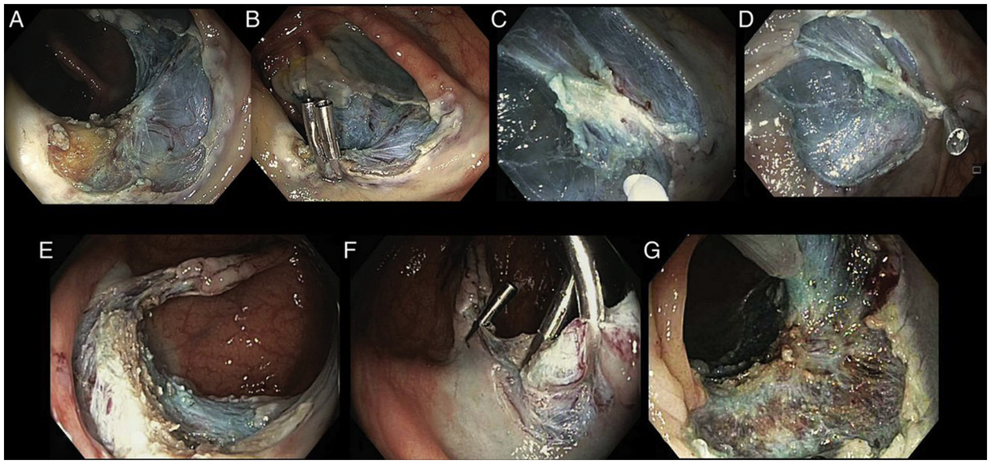

Fig. 7. In a 'type II' defect, the distinction between submucosa and muscularis propria is unclear often due to poorly staining submucosal fibrosis. (A) In this image, an area of poorly staining defect and submucosal fat is noted following snare resection. (B) Two clips are placed over the area of concern. (C) A focal area of fibrosis is noted following resection of a 30 mm caecal lesion. The area is interrogated by topical application of dye staining via an injection catheter with the needle retracted, however, it remains unstained. Clips are then placed across the area of concern. The first clip is shown in-situ; further clips were subsequently placed to close the entire fibrotic area. (E, F) An area of poor staining overlying a fold is treated with three clips. (G) This defect has a central area of fibrosis and cautery effect impairing the assessment of deep injury.
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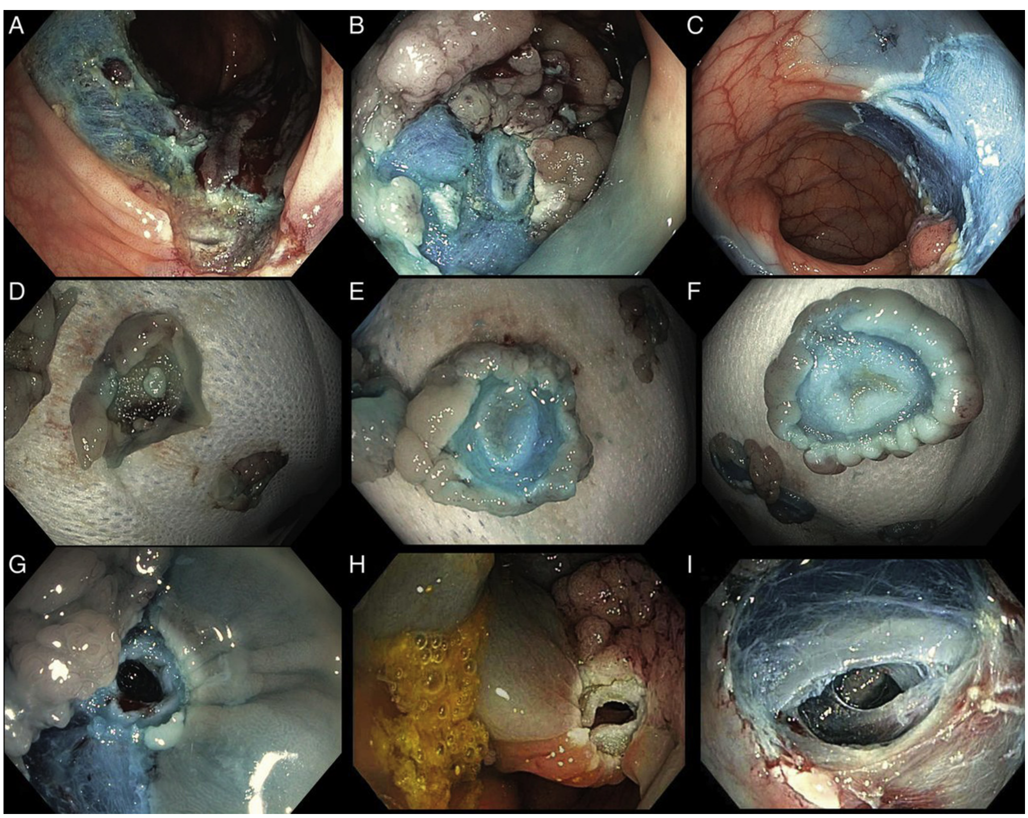

Fig. 8. A 'type III' defect refers to partial resection of the muscularis propria resulting in a defect target sign (DTS) (A, B, C) or a specimen target sign (D, E, F). These defects require clip closure of the DTS to prevent delayed perforation. A type IV defect is a complete hole, or full-thickness resection of the muscularis propria which is clean and not contaminated by faecal effluent. (G, H, I) A concentric ring of cautery artifact to the muscularis is observed. These defects should be closed immediately, although resection of the surrounding adenoma prior to clip placement should be performed where possible. If the closure site is not clear of adenoma, follow-up attempts at resection may be hampered by submucosal fibrosis, clip artifact and buried adenoma. A type V defect occurs where the full thickness perforation is contaminated by faecal effluent. These defects should also be closed and a surgical consultation obtained. Acute surgical intervention is required if there is clinical deterioration, features of peritonitis, evidence of significant free intraperitoneal fluid or failed endoscopic resection.
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have reported IBP about 2.8% [69] from all the polypectomies. In addition a meta-analysis from 50 studies have reported overall bleeding rate after EMR about 6.5% (95% CI 5.9% to 7.1%) [57].

Homeostasis after IPB is usually controlled by thermal modalities with the use of voltage-limited current to avoid the deep injury. STSC (snare tip soft coagulation) has been demonstrated to be a good technique to control bleeding. It is safe, quick, inexpensive and simple method to perform [68]. This skill involves the use of snare tip of 2–3 mm beyond the catheter and application of coagulation current at the same time as gently stroking the tip directly into the point of bleeding. Rigorous washing clears the resected field and helps in localization of the bleeding vessels. In addition this technique also will create a tamponade effect and protecting the deeper layers [70]. In cases where homeostasis is not maintained with STSC, use of TTS clips or coagulating forceps is recommended. Use of coagulation graspers is recommend when the bleeding vessel is large (typically >1–2 mm) or STSC fails. The forceps are applied the bleeding point and it is grasped and tented toward the lumen to avoid the deep tissue injury, followed by use of soft coagulation current for 1–2 s.

Delayed bleeding

Delayed or post procedural bleeding (termed as clinically significant post endoscopic bleeding (CSPEB) is defined as any bleeding occurring up to 30 days after EMR resulting in emergency room presentation, hospitalization or requiring re-intervention [71]. Delayed bleeding is mostly seen in patients with age >65 years old, those on anticoagulants, and proximally located lesions [72–74]. Results from the study by Burgess et al. have reported about 6.2% cases of CSPEB and was significantly associated with lesions located at proximal colon, IPB, and use of electrosurgical current not controlled by microprocessor and. Patient comorbidities and lesion size did not predict the CSPEB [71]. Most of the time management is conservative and very rarely requires embolization at angiography or surgery. In a multicenter study by ACE group (Australian Colonic Endoscopic group), cohorts of 1039 patients with wide-filed EMR were included. Clinically significant bleeding was found in 6% of cases and of which 55% were managed conservatively [67]. Moderate or severe bleeding was associated with hemodynamic instability, and low hemoglobin at presentation. Hemostasis intervention was significantly associated with hourly or more frequent haematochezia, American Society of Anesthesiologists (ASA) grade 2 or higher and need for transfusion [67].

In one RCT, routine prophylactic endoscopic coagulation of non-bleeding vessels did not decrease the incidence of CSPEB [75]. However in one retrospective study use of low-power coagulation current and prophylactic clipping of the resection sites after EMR of large polyp's ≥2 cm reduced the risk of delayed bleeding. 9.7% in the not clipped group vs 1.8% in the fully clipped group had delayed hemorrhage. On multivariate analysis; proximal location, use of no clip, and larger polyps were associated with delayed bleeding. Mucosal defect closure is considered for the high risk cases; however it should be individualized based on the patient factors [76]. In one of the multicenter observation study, clipping was found to be protective factor for high risk patients [77]. RCTs published to date have conflicting results. Three prospective RCTs have been published: One of them did not show beneficial effects and other 2 have shown positive results [77–80]. Thus, well designed multicenter randomized controlled trials are yet be established to answer the question; whether prophylactic clipping of EMR defects improves the risk of bleeding or not. Scoring system has been developed to determine the risk of CSPEB post EMR of colorectal polyps [77,81].

Post polypectomy electrocoagulation syndrome and delayed perforation

PPES is defined as an injury to the bowel wall that makes a deep burn and contained peritonitis causing a serosal inflammation [82]. The incidence of PPES varies between 0 and 7.6% but most of the studies report around 1%. The typical presentation may be limited abdominal pain, fever and peritoneal signs associated with increased level of C-reactive protein, leukocytosis in lab investigations and absence of perforation on radiologic imaging. Polyp size >20 mm, right sided EMR, hypertension and non-polypoid lesion morphologies are the major risk factors for PPES [83,84]. Patients may present within few hours to 7 days after the EMR. Most of the time the treatment is conservative like bowel rest, antibiotics and use of intravenous fluids. Most patients improve within 24 h without any consequences; however it is very important to monitor closely to make sure that symptoms don't get worse.

Delayed perforation though rare; but, like PPES it is believed to be initiated by a thermal injury. Most patients present within 24 h but may occur more than a week later, and when suspected, may require further evaluation by CT scan to establish the diagnosis and confirm perforation [85]. If perforation is confirmed surgical repair is warranted [86].

Recurrence after endoscopic mucosal resection

Recurrence of adenoma is one of the important longer-term complications of PEMR. Large sessile colorectal polyps larger than ≥2 cm in size has a higher risk to harbor or progress to cancer [87]. Although PEMR has been established as a minimally invasive technique for treatment of large colorectal polyps, risk of recurrence of residual polyp at first follow up ranges form 0–55% with an mean recurrence rate of 25% [88]. In a multicenter, prospective study by ACE group which included 799 patients with completed first SC1, rate of recurrent/residual adenoma was present in 16% patients. On multivariate analysis, risk factors for early recurrence were size >40 mm, use of APC, and intraprocedural bleeding [89]. Similarly, results from same group have shown that high grade dysplasia (HGD) was also associated with early adenoma recurrence in addition to size ≥40 mm and IPB [90]. Factors like large lesions (≥4 cm), use of APC and incomplete submucosal lifting are associated with incomplete or failed PEMR [89,91,92]. Thus EMR experts should give emphasis on complete resection and careful attention of large lesions (>40 mm) rather than ablation of adenoma with APC.

Late adenoma recurrence is defined as an adenoma identified at second follow up examination after an initial unremarkable tissue and negative scar histologically [93]. The rate of late recurrence was about 22.1% in a study by Kanbe et al. and was not related with original size of the lesions. The resection technique had important impact on the rate of recurrence especially in the right colon [93]. On multivariate analysis, only significant variable associated was resection technique. Lesser recurrence was associated with en-bloc than PEMR technique. There was no benefit of APC use with regard to residual lesions [93]. In another multicenter prospective study the rate of late recurrence (SC2 at 16 months) was reported about 4% (95% CI, 2.4–6.2%) [89]. However endoscopic management of recurrent lesions was successful in about 93.1% cases.

Technique to decrease adenoma recurrence

PEMR is an established technique with an excellent safety profile for removal polyps greater than 2 cm. Results from several studies have demonstrated high success rates with minimal morbidity and mortality. Several heat based techniques have been applied in an attempt to “destroy” any remaining polyp either in the index EMR or during the follow up. Examples included immediate thermal ablation of visible polyp remnants with the tip of snare, delayed electrocoagulation of polypectomy site at 3–4 weeks after polypectomy, ND: YAG laser, with the application of APC or extended resection of EMR margins [59,94–98].

In one large prospective, multicenter study 71.7% cases had diminutive residual/recurrent adenoma on SC1 [89]. Overall, recurrence was managed endoscopically in 93% cases. Adjunctive use of APC for ablation of visible residual adenoma not able to remove by snare resection has been consistently identified as major potentially modifiable risk factor for recurrence [13,89]. Avulsion is a new technique to treat visible neoplasia during EMR. This technique involves use of forceps and microprocessor-controlled current to remove the residual areas of adenomatous mucosa or post EMR margins which is not amenable to snare resection during EMR [34,45,59]. It should be distinguished to hot biopsy sampling, a technique in which coagulation current is delivered with a forceps to ablate small polyps. A retrospective study by Holmes et al. compared the recurrence of adenoma on follow up on use APC vs avulsion during index EMR [46]. The adenoma recurrence rate was significantly lower in avulsion group than those treated with APC (10.3% vs 59.3%, OR, 0.79; $p < 0.001$) [46]. No significant difference was observed in rates of adverse events.

Adenoma recurrence has remained an important limitation of PEMR technique. Residual polyp may occur in EMR margin due to inconspicuous adenoma presence and margins not appreciated at the conclusion of EMR. Hypothetically extending the resection margins by at least 5-mm may remove the microscopic adenoma at margins and decrease the rate of recurrence in a follow up. However, the results from Bahin et al. have reported that there was no difference in rate of recurrence between standard EMR and extended EMR groups (11.7% vs 10.1%, $p = 0.15$) [59]. Extended EMR was not related to recurrence (HR, 0.8; 95% CI, 0.5–1.3; $p = 0.39$).

Adjuvant thermal ablation of EMR margins may reduce the adenoma recurrence. Endoscopically invisible micro-adenoma present at the margins could be destroyed by thermal ablation or coagulation of margins. Preliminary results from a multicenter study have reported that thermal ablation of the margins of the post EMR defect with snare tip soft coagulation (STSC) significantly reduce the adenoma recurrence rates in first SC1 [99]. About 768 lesions ≥20 mm were randomized 1:1 to either thermal ablation of the defect edges using snare tip soft coagulation (STSC) at 80W effect 4, or no additional treatment. SC1 was performed at 5–6 months. Endoscopic and histologic recurrences at SC1 were significantly lower in STSC group compared standard EMR group (5.8% vs 20.2%, $p < 0.001$) and (5.8% vs 20.6%, $p = 0.002$). Endoscopic assessment of the post EMR scar had sensitivity of 100% and negative predictive value of 100% for correctly identifying the recurrence. There no difference in delayed bleeding between STSC group and Standard EMR group [99]. Although preliminary data looks very promising, external validation of these results is yet to be established (Tables 3 and 4).

EMR follow up guidelines

A well-structured surveillance program is required to decrease potential patient morbidity, additional costs and repeated procedures that could create compliance burdens. Most recurrences are found in first follow up and 90% are detected in first 6 months after PEMR [107]. However, complete removal can be achieved in >90% of local recurrences with only one time endoscopic re-treatment and bulk of patients have total remissions on EMR follow up [89]. There are no optimal guidelines and timing for the first follow up colonoscopy after index EMR. Current strategies suggest follow up at 3–6 months after endoscopic resection, but subsequent follow up plans is unclear [108–110]. However available data have shown that an initial surveillance colonoscopy at the interval of 6 months is adequate for recurrent adenoma detection than an interval at 3 months [107]. In a prospective multicenter cohort by David et al. has developed a scoring system to stratify the surveillance strategy and the risk of residual or recurrent adenoma (RRA) after piecemeal EMR. A scoring system was called Sydney EMR recurrence tool (SERT) which was developed after logistic regression model for endoscopically determined recurrence (EDR). Scores were allocated to 2,1 and 1 for the lesion size >40 mm, bleeding during the procedure, and the high grade dysplasia which were identified as independent predictors for EDR [90]. SERT stratified the incidence of RRA and surveillance follows up after EMR. Patients with SERT = 0 lesions could undergo first surveillance at 18 months where was lesions with SERT scores between 1 and 4 (SERT1-4) could be followed up at 6 and 18 months. Although the data looks very promising and encouraging but do have several limitations. Results were drawn from centers where the rate of recurrence of adenoma is very low compared to other high volume centers where most of the patient's referrals are from community gastroenterologists. In those cases, most lesions are previously manipulated (either by hot or cold biopsy) which make complete resection difficult during index EMR due to submucosal fibrosis. Thus, follow up is required at least at 3–6 months intervals. In that scenario following up at 18 months even for SERT = 0 lesions won't be a genuine approach. In addition study data were derived from a tertiary-care referral center which limits the applicability of this method for EMR experts outside this context. In addition external validation of results has yet to be established.

Imaging protocol in recurrent adenoma detection after EMR

According to the current guideline first follow up after PEMR should be conducted at the interval of 3–6 months to make sure adequate detection and treatment. Optical detection of recurrent adenoma endoscopically during follow up colonoscopy is possible with improved imaging technologies. Traditionally all the EMR scars are biopsied during follow up. Addition of imaging technology may help improving the targeted biopsy sampling and avoiding inadequate samples, which may lead to inadequate assessment. However, optical diagnostic accuracy in detecting RRA is believed to be low [13,111].

In a large prospective study by Desomer et al. have demonstrated that HD NBI detects more flat dysplasia with improved

Table 3
Different techniques to decrease adenoma recurrence after PEMR.

Author/study year	Study type	Total number of patients	Technique	Recurrence	P value
Holmes et al., 2016 [46]	Retrospective	278	Use of avulsion for residual tissue during EMR vs APC use	10.3% for avulsion use vs 59.3% for use of APC	0.01
Bahin et al. [59]	Prospective	396	Extended resection of EMR margins (at least 5-mm margin of normal mucosa) vs only standard EMR.	11.7% for standard EMR (S-EMR) vs 10.1% for extended EMR (X-EMR).	0.1
Klein et al. [99]	RCT	359	Use of snare tip soft tissue coagulation (STSC) of post EMR margins vs only standard EMR.	5.8% for STSC vs 20.6% for Standard EMR.	0.002

X-EMR: extended EMR, APC: Argon plasma coagulation; EMR: endoscopic mucosal resection; STSC: snare tip soft tissue coagulation, RCT: randomized controlled trial.

Table 4
Various studies evaluating outcomes by EMR technique on large colorectal polyps.

Author (year)/(country)	Study design	No. of patients	No. of lesions	Success rate	Bleeding rate	Perforation	PPPS	Recurrence rate (piecemeal only)	Follow up (mean months)
Margagnoni, 2016 [91]. Italy	Retrospective	125	141	98.5%	0.7%	0.7%	NR	23.4%	9
Tate et al., 2016. Australia	Prospective, Multicenter	2384	2204	93.9%	IPB: 4% Delayed: 2%	NR	NR	Early: 19.4% Late: 4.9%	SC1 = 4.9 SC2 ≥ 16
Moss et al., 2015 [89]. Australia	Prospective, Multicenter	1134	1000	88%	NR	NR	NR	Early: 16% Late: 4%	SC1 = 4 SC2 = 16
Binmoeller et al., 2015 [54]. USA	Prospective, single center (*Underwater EMR)*	50	53	100%	IPB: 1.8%	0%	1.8%	3.7%	31
Oka et al., 2015 [100]. Japan	Prospective, multicenter	808	808	NR	IPB: 1.4%	0.9%	0%	14.5%	<12
Kashani et al., 2015 [50]. USA	Retrospective	97	124	91%	IPB: 3.9% Delayed: 2.4%	3.9%	0%	12%	4.2
Curcio et al., 2015 [52]. Italy	Prospective, Multicenter, *(Underwater EMR)*	79	81	100%	0%	0%	0%	0%	3
Gomez et al., 2014 [101]. USA	Retrospective	99	131	94%	2.3%	3%	0%	17%	NR
Magurie and Shellito, 2014 [102]. USA	Retrospective	231	269	89.1%	2.6%	1.1%		24%	
Terasaki et al., 2012 [103], Japan	Prospective, Single center.	178	178	100%	8.4%	1.7%	NR	12.1%	21.5
Fasoulas et al., 2012 [40]. Greece	RCT	49	49	100%	14.2%	2%	4%	24%	34
Kim et al., 2012 [104]. Japan	Retrospective	488	493	93.7%	2%	0.4%	0.4%	2.9%	12
Conio et al., 2010 [105]. Italy	Prospective, Multicenter	255	282	94%	0%	0%	0.3%	4% (enbloc)	
Ferrara et al., 2010 [106]. Italy	Prospective, Single center	157	177	100%	1.1%	1.1%	2.2%	6.4%	19.8

EMR: endoscopic mucosal resection; IPB: intraprocedural bleeding; SC1/SC2: Surveillance colonoscopy 1 and 2; NR: not reported.

accuracy compared to white light alone [112]. Six of 8 cases (75%) of flat lesions were detected by NBI alone at first SC1 in 3–6 months. They have shown the value of NBI over white light in detection of tissue characteristics and margin assessment in post EMR scars in real time which may modifies the management at the time of procedure. In this study all EMR scars were evaluated with HD-WL and NBI with careful inspection of pit and vascular patterns (neoplastic vs non-neoplastic pit patterns). Among 183 EMR scars were evaluated, 16.4% post EMR scars had histologically confirmed RRA at SC1 where as 20.2% post-EMR scars were suspected to have RRA endoscopically. There was no statistical significance among predicted and histologic outcomes ($P = 0.65$). Applying imaging protocol (HD-WL + NBI), the sensitivity of endoscopic detection of RRA was 93.3%, negative predictive value (NPV) was 98.6%, and diagnostic accuracy was 94%. Sensitivity is increased after addition of NBI as opposed to HD-WL alone (66.7% vs 93.3%) [112] (Figs. 9 and 10). Adoption of new technology and technique like NBI helps in distinguishing adenomatous tissue from non-adenomatous tissue by careful inspection of the color, mucosal patterns, and vessels patterns [113]. Assessment scars of in real time helps in accurate recurrent adenoma detection that allows the appropriate treatment with thermal ablation/or snare excision minimizing the risks and cost involved in such treatment.

On the other hand we have evidence indicating that the 2nd generation HD NBI system may be highly accurate for detection of RRA at follow up colonoscopy. An ongoing prospective double-blinded trial by Kandel et al. have shown preliminary data, indicating very high negative predictive value (NPV) and good diagnostic accuracy with HD NBI near-focus system for optical detection of residual neoplasia in both: real-time and offline evaluation. Per-protocol 107 patients with 111 scar sites were evaluated. Sensitivity was 100% (95% CI 89–100) and NPV was 100% (95% CI 94–100) for HD NBI near-focus with high confidence at real time. The diagnostic accuracy was 94% and 92% for HD-NBI near-focus both online and offline with high confidence diagnosis. The interobserver agreement for NBI near-focus was substantial (kappa: 0.81 95%-CI: 0.68–0.94) among five experienced EMR endoscopists who were blinded to histopathology results and assessed the EMR scar offline. Therefore, these advanced imaging modalities may improve real-time decision making in follow-up after colorectal EMR, particularly the avoidance of biopsy (Kandel et al., 2017 [121]). Diagnostic accuracy of optical detection of colorectal neoplasia after endoscopic mucosal resection: prospective double blind comparison of high definition white light, narrow band imaging and near focus. GIE, Press.

Clip artifacts: a difficult task for post-EMR follow up

PEMR is a standard practice for the treatment of large colorectal polyps. Clipping is an effective technique for management of deep mural injuries and intraprocedural bleeding. The incidence of IPB is about 2.5% to 11% and risk of perforation is about 0.5% to 4% after PEMR [114]. But there is lack of evidence and conflicting results regarding the benefit of prophylactic clipping in reducing bleeding risk. Many endoscopists prefer closing the EMR defect with clips. The fate of clips after healing of defect is undetermined: either they fall apart within a few weeks and expelled from body or retained in for long time. The healed mucosal scar is distorted and gives a different appearance of the scars. This limits the accurate evaluation of recurrent adenoma at the EMR scar sites. The endoscopic diagnosis may give high false positive rates, and therefore often warrant biopsy of scar tissue for accurate diagnosis. Post EMR clip artifacts (ESCA) are difficult to distinguish from recurrent polyps. ESCA is illustrated by a nodular rise of the mucosa with a normal pattern which can occur with or without

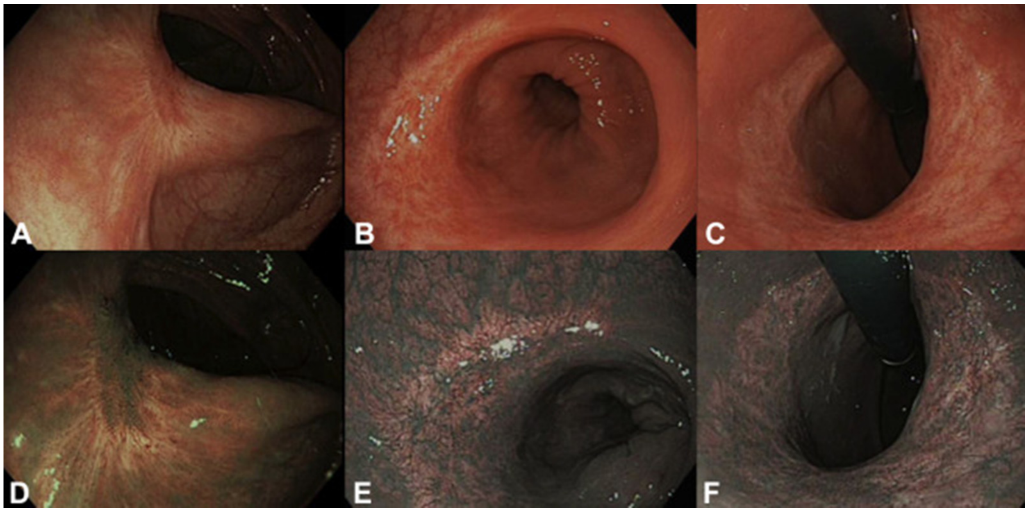

Fig. 9. EMR scars visualized with high-definition white light and narrow-band imaging (A–F).
Adapted from Desomer and colleagues (Desomer et al., 2017, GIE. 2017; 85 (3): 518–526) with permission from Elsevier.

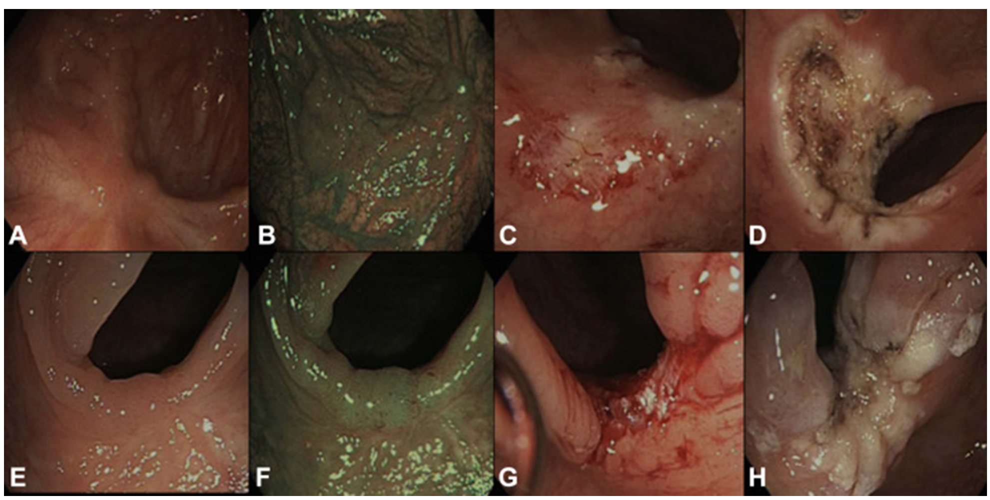

Fig. 10. Recurrent adenoma visualized with high-definition white light and narrowband imaging (A–F). Recurrent adenoma treated with snare polypectomy and thermal ablation.
Adapted from Desomer and colleagues (Desomer et al., 2017, GIE. 2017; 85 (3): 518–526) with permission from Elsevier.

residual clips [115] (Figs. 11 and 12). In one single center prospective study ESCA was present in 46.8% with in a follow up of 5.2 months. ESCA was present in lesions which were clipped for prophylactic bleeding control than those clipped for deep mural injury or IPB (65.5% vs 41.7%, P = 0.006). Greater age and female sex was associated with ESCA [115]. Adenoma recurrence was present in five cases with clip artifact. Assessment of post EMR scars is challenging because of the nodularity due to granulation tissue and coexistence of adenoma in the same scar. It is very important to investigate closely each bump (regarding vessels and pit patterns) to avoid misdiagnosis and overtreatment. It is often recommended to remove the retained clips to enable accurate investigation of site. In one retrospective study adherence rate of hemoclips placed after large colorectal EMR was evaluated. Retention rate of two different types of clip was assessed (Boston Scientific Resolution clips vs Cook Instinct clips). 4.2% of Boston Scientific Resolution clips were retained vs 8.6% for Cook Instinct clips in first follow up intervals, (P = 0.001). There was no difference in the follow up interval for the 2 clips. No residual polyp was found at the base of retained clip [116]. It may be interpreted as longer retention clips on the site means more effective closure, and might have better prevention of hemorrhage.

Economic analysis: EMR vs surgical approach

EMR is a standard management for large colorectal polyps. Although the technique is very safe and effective, patients still are referred for surgery because of fears over adenoma recurrence and incomplete resection after EMR. There are few studies that have evaluated the cost-effectiveness and outcomes comparing EMR and surgical management of large colorectal polyps [117–120]. In one study by Law et al. compared cost effectiveness between the EMR and laparoscopic resection of large colorectal polyps. Results have shown that laparoscopic resection was more expensive and fewer quality-adjusted life years (QALYs) in comparison to EMR ($18,717/patient and 9.57 QALYs versus $ 5570/patient and 9.64 QALYs) [118]. In subgroup one-way sensitivity analysis the hybrid Markov model was most profound to methodological success (75.8%), cost of laparoscopic resection ($14,000) and adverse event rates (>12%). In addition Australian Colonic Endoscopic Resection study group

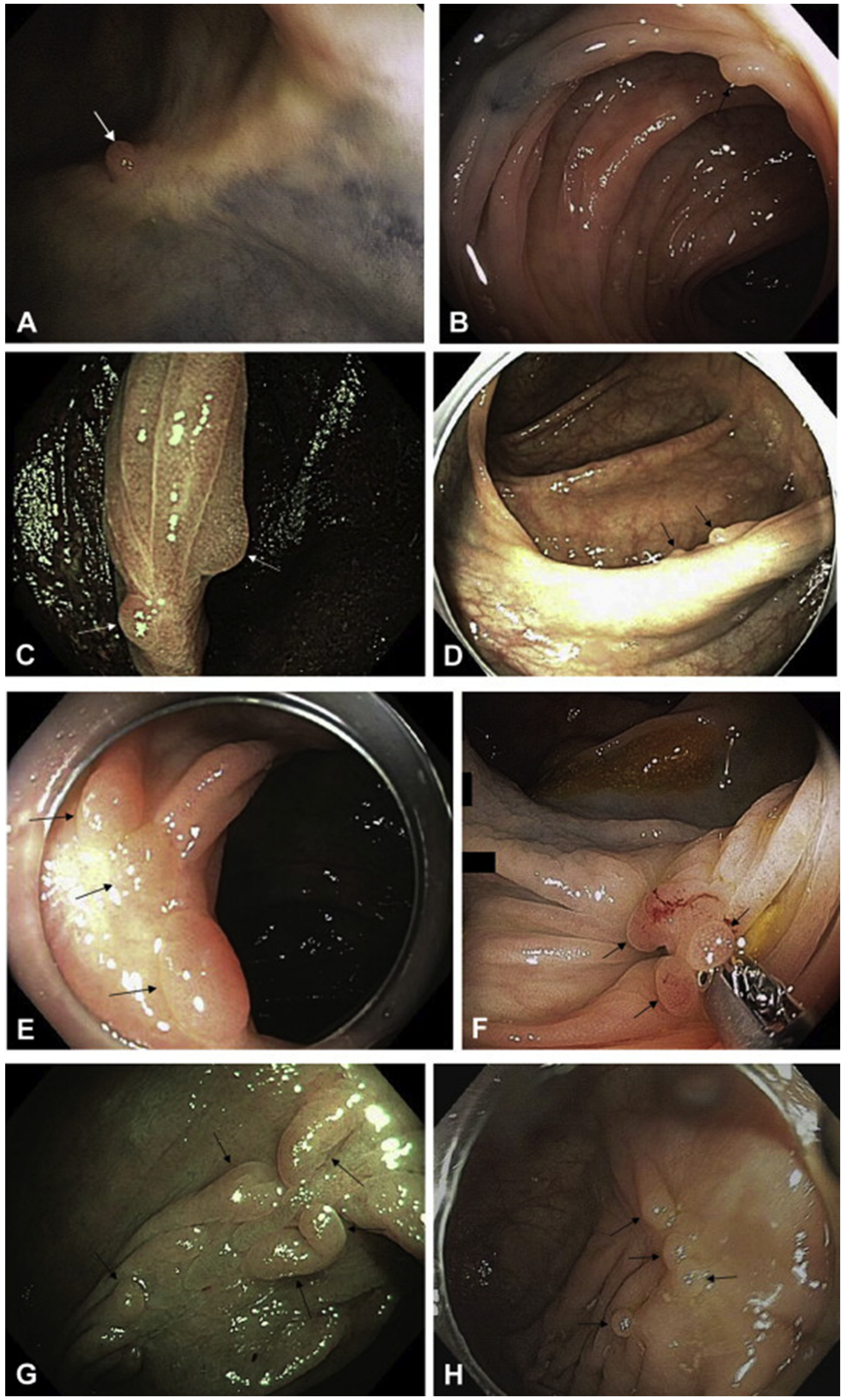

Fig. 11. EMR scar with a clip artifact. Arrows in image label the clip artifact.
Adapted from Sreepati and colleagues (Sreepati et al., 2015, GIE. 2015; 82 (2): 344–349) with permission from Elsevier.

also reported similar results with cost savings of >$7500/patient when EMR approach is followed instead of surgery [120]. Data from large SEER database have shown mid- and long-term colorectal cancer-free survival rates between endoscopic and surgical management of stage 0 and (Tis) malignant colorectal polyps [117]. Financial burdens associated with surgery are high. When costs of EMR for large colorectal polyps of more than 1300 patients in one multicenter prospective study including all adverse events and surveillance requirements were modeled against surgery with the best possible adverse event-free outcome, EMR was found to be significantly cost-effective than surgery. The mean cost difference per patient was found to be U.S $ 7602. Hospital inpatient length was reduced by 2.81 days per patient in favor of EMR [120]. Thus all the available data regarding the safety, efficacy and cost

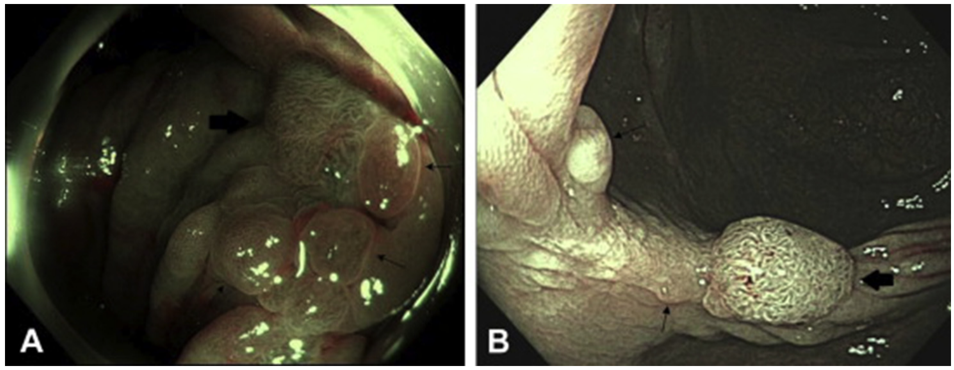

Fig. 12. EMR scars demonstrating the clip artifact and residual adenoma (Image A: thin arrow > clip artifact, Image B: thick arrow > residual adenoma). Adapted from Sreepati and colleagues (Sreepati et al., 2015, GIE. 2015; 82 (2): 344–349) with permission from Elsevier.

effectiveness make strong reason for endoscopic management as a first line treatment for large colorectal polyps (adenomas and SSA/Ps) by expert endoscopists.

Practice point

1. EMR is a standard management for large colorectal polyp.
2. Recurrent adenoma is managed successfully with greater than 90% success with repeat EMR on follow up.
3. Argon plasma coagulation should not be used for adenoma ablation during index EMR.

Research agenda

1. Well-designed techniques are necessary to decrease the adenoma recurrence on follow up.
2. Well-designed trials are necessary to see the benefit of near focus mode (either white light or narrow band imaging) for post EMR scar assessment.

Conclusion

EMR is a safe and effective for the management of large colorectal polyps with low and acceptable adverse events. Although the risk of adenoma recurrence is a main morbidity of PEMR, but recurrent adenoma is managed successfully in >90% of the cases during follow up. The recommendation of surgical approach or endoscopic mucosal resection is approached by evaluating the risk of lesion invasion or malignancy. All the lesions should be avoided extensive biopsies if a patient is referred for polyp removal at tertiary high volume center for complete resection.

Conflicts of interest

Michael Wallace reports grant support from Boston Scientific, Medtronic, Cosmo pharmaceuticals, and equity interest in iLumen. Dr Wallace is a consultant to Aries Pharmaceuticals and Lumendi Inc. None of these entities are discussed in this article.

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