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Efficacy and Safety of a Novel Triple-anchoring Technique for Colonic Hybrid Endoscopic Mucosal Resection: A Case Series

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ABSTRACT

Background & Aims: A hybrid technique may be a reasonable compromise to make endoscopic mucosal resection (EMR) more reliable for lesions ≥ 20 mm and a good way of approaching to endoscopic submucosal dissection (ESD). The aim of this study was to assess the efficacy and safety of a novel hybrid EMR technique, triple-anchoring EMR (T-EMR) for colorectal lesions 20-30 mm.

Methods: Fifteen patients have been prospectively enrolled to T-EMR from December 2019 to April 2020 in two Endoscopy Units: Policlinico A. Gemelli, Rome, and University Hospital of Udine, Italy. Patients eligible for the study were ≥18 years old with superficial colorectal lesions 20-30 mm, morphologically liable to endoscopic treatment based on chromoendoscopy. The primary endpoint was assessment of the "en bloc" and the free resection margins (R0) rates. The secondary endpoints were resected specimen size, procedure time, complication rate, and recurrence rate at 6 months.

Results: Among the 15 patients enrolled, 12 were males (80%), mean age 68.73±11.04 years. The mean size of the lesions was 24.93±2.89 mm. Mean procedure time was 22.13±4.31 min. T-EMR was performed en bloc in 14/15 patients (93.3%) with R0 in 13/15 patients (86.7%). No major intra-/peri-procedural or delayed complications occurred. At histological analysis, 13/15 lesions (86.7%) were adenomas, while 2 were early colorectal cancer. At a 6-month follow-up colonoscopy, only one patient (6.7%) had a recurrence of adenoma.

Conclusions: T-EMR seems to be an effective and safe option to treat colorectal lesions between 20 and 30 mm, with a short procedure time and low costs.

Key words: colorectal polyps – endoscopic mucosal resection – EMR – hybrid technique – triple-anchoring EMR.

Abbreviations: ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; NBI: narrow band imaging; R0: free resection margins; T-EMR: triple-anchoring EMR.

INTRODUCTION

Superficial colorectal lesions smaller than 20 mm in size can be safely removed en bloc by endoscopic mucosal resection (EMR). On the contrary, larger lesions (≥ 20 mm) usually require a piecemeal EMR [1] that is related to a lower curative rate [2] and to a higher risk of recurrence [3-5]. Sometimes, also lesions smaller than 20 mm in size can be hard to treat by EMR because of a difficult location (for example backside of folds, corners, areas near a diverticulum) and/or because of the presence of a non-lifting sign [6, 7]. Moreover, when a superficial invasive carcinoma is suspected, an en bloc resection is crucial to assess by hystology if the endoscopic treatment has been curative [3].

Endoscopic submucosal dissection (ESD) was developed in Japan in the mid-1990s to resect en bloc early-stage gastrointestinal lesions, regardless of their shape and size. However, ESD is a technically demanding procedure which requires a long training and an expertise hardly reachable in Western countries. Moreover, ESD not only requires a longer procedure time, but it is also related to a higher risk of perforation and bleeding compared to EMR [2, 8, 9].

Over the years some modifications of the classical EMR technique, such as underwater EMR, have been proposed in order to improve EMR perfomances and to make outcomes comparable to those of ESD [10]. However, despite some improvements wich have been noted in other outcomes, lower

en bloc resection rate still maked EMR inferior to ESD when treating lesions larger than 20 mm [10]. Nevertheless, ESD and EMR are not mutually exclusive, and a hybrid technique may be a reasonable compromise to make EMR more reliable by enabling larger polyp pieces to be resected obtaining a clear lateral margin to allow a better histopathological assessment of the specimen and to make ESD easier and quicker [6, 11-13]. The hybrid technique can also represent a good transitional way of learning ESD for Western endoscopists.

The aim of this study was to assess the efficacy and safety of a novel technique of hybrid EMR, triple-anchoring EMR (T-EMR) [14] for the treatment of colorectal lesions between 20 and 30 mm in size.

METHODS

Fifteen adult patients were prospectively enrolled to undergo hybrid T-EMR from December 2019 to April 2020 in two Endoscopy Units: Policlinico Agostino Gemelli, Rome, Italy, and the University Hospital of Udine, Italy. The study design was approved by the local Ethics Committee (Prot. ID 3896; Prot. N. 0010167/21).

Patients eligible for the study were adults (≥18 years old) with superficial lesions between 20 and 30 mm in size (lesion size calculated by visual estimation), located in the colon and rectum, morphologically liable to endoscopic treatment based on either narrow band imaging (NBI) (Olympus Medical Systems Tokyo, Japan), or i-SCAN (Pentax Inc, Tokyo, Japan) analysis, or chromoendoscopy with indigo carmine. Patients affected by coagulation problems (such as platelet <30,000/mc/L, INR >1.5), chronic kidney disease, heart disease, lesions >30 mm, lesions not liable to endoscopic treatment (suspected deep submucosal invasion with endoscopic features of expansion appearance, deeply depressed surfaces with irregular bottoms, converging folds toward the tumor, type V_N pit pattern, tumors showing non-lifting signs), patients who did not give their consent to the enrolment in the study, patients suffering from any condition which precluded compliance with study instructions, patient having any allergy or other known contraindication or intolerance to the medications used in the study for the bowel preparation or colon staining, pregnant or nursing women, patients with concurrent participation in another clinical trial using any investigational drug or device, and patients suffering from a life threatening condition were excluded.

Patients were enrolled during diagnostic colonoscopy performed for a positive fecal occult blood test (FOBT) or other indications (such as rectorrhagia, constipation, colorectal cancer familiarity).

After informed consent was obtained, hybrid T-EMR was performed by three skilled endoscopists in the EMR procedure. All procedures were performed in conscious sedation (with midazolam and fentanyl). Sequential steps to perform hybrid EMR were done as follows (Figs. 1, 2): 1) measurement of colonic/rectal lesions through an open 6 mm biopsy forceps; 2) injection of a solution of diluted epinephrine (1:200,000), indigocarmine and glycerol under the lesion, at the top (2 mm above) and then all around the lesion, to lift the submucosa; 3) creation of a hole at the top of the lesion with the tip of the snare pulled out 2 mm out of the catheter; 4) creation of a small cut with the 2 mm tip of the snare on the right and left side of the lesion; 5) opening the snare, hooking it into the apical hole and then closing it slowly and partially in order to reduce the size of the snare itself; 6) snare placement into the small cuts on the right and left side of the lesion and further snare closure; 7) lumen inflation before cutting the tissue (in order to avoid catching the muscular layer); to cut the lesion, coagulation mode was used first to verify if the patient felt any sharp pain, then, cutting mode was used; 8) ulcer closure by clips placement.

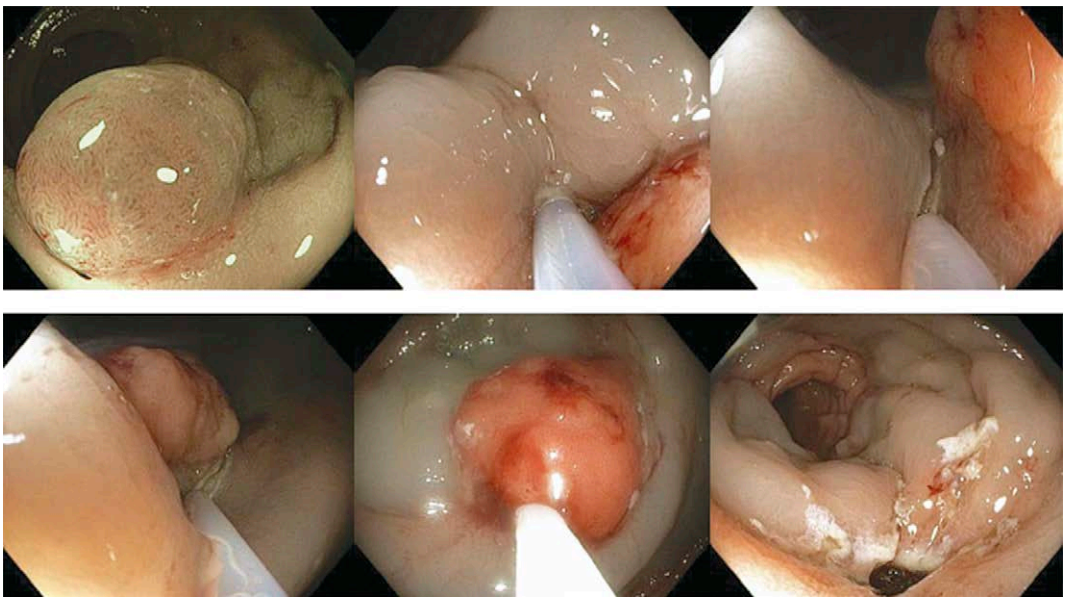

Fig. 1. Endoscopic images showing: A. a large colonic polyp in the rectum suitable for endoscopic mucosal resection by the triple-anchoring technique; B, C, D. small incisions on the top and on the lateral margins of the lesion, which were made using the tip of the snare in Endocut mode; E. the 25-mm snare grasping the lesion with the triple-anchoring technique; F. the resected area following en bloc capture of the entire large polyp, consistent with macroscopic complete resection.

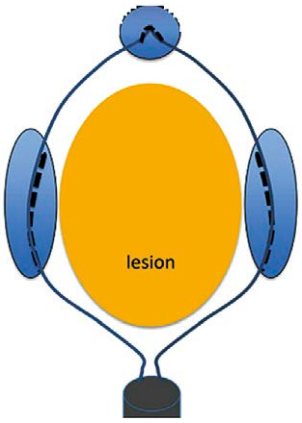

Fig. 2. The three sites of snare fixing (triple-anchoring) in order to catch the lesion avoiding its slipping.

The snare used for the procedure was a 25 mm disposable snare, the "Snare Master" by Olympus; ERBE VIO 300D (ERBE electromedical, Tubingen, Germany) was the electrosurgical unit employed for cutting with Endocut Q, Effect 3 (duration 2, interval 3) and Forced Coagulation Effect 2 50W as standard settings. The same elecstrocauthery settings were used in all the lesions irrespective of the localization in the colon. The colonoscopes used were single-channel Pentax Medical EC38-i10F or Olympus CF-HQ190i. Carbon dioxide was used for insufflation.

All patients subjected to T-EMR were reviewed by a multidisciplinary team including a gastroenterologist, an expert pathologist in gastrointestinal pathology, and, when necessary, a surgeon. A follow up colonoscopy with biopsies at the site of the post-polypectomy scar to assess any potential macroscopic and histological recurrence was performed 6 months after T-EMR.

The primary endpoint of this study was assessment of the en bloc resection rate and of the R0 curative resection rate. The secondary endpoints were the resected specimen size, the procedure time, the complication rate, and the recurrence rate (6 months later) of the lesion. Procedure time was defined as the period from the first mucosal incision to completion of the ulcer closure by clips placement. Major acute or delayed (up to three months after the procedure) complications were defined as perforation, bleeding requiring transfusion, emergency endoscopic evaluation and/or surgical procedure, and any complication requiring hospitalization. Minor complications were defined as minor bleeding or small perforations occurring during T-EMR and effectively treated during the procedure, not requiring hospitalization.

Microsoft Excel was used for collecting data, proportions and effect size. The other statistical analysis was performed with IBM SPSS version 23. A two tailed Student's *t* test was used to compare groups, and differences were considered to be statistically significant when the p value was less than 0.05. Effect size was measured with Cohen's *d*. Bivariate correlation was evaluated with two-tailed Pearson correlation coefficient and it was considered significant at 0.05 level.

RESULTS

Between December 2019 and April 2020 fifteen adult patients were prospectively enrolled to undergo hybrid T-EMR in two Endoscopy Units, Policlinico Agostino Gemelli, Rome, Italy, and University Hospital of Udine, Italy.

Table I summarizes the demographics of the patients selected and the site and size of the polyps, while their Kudo classification is shown in Table II. Most lesion were localized in the cecum (3, 20%), sigmoid colon (3, 20%) and rectum (3, 20%) followed by ascending colon (2, 13.3%), transverse colon (2, 13.3%) and descending colon (2, 13.3%)

Table I. Patients' demographics; polyps' site and size

Gender (F:M)	3 : 12
Age at procedure (years ± SD)	68.7 ± 11
Site of lesion (right colon: left colon)	6 : 9
Size (mm ± SD)	24.9 ± 2.9

Mean procedure time was 22.13±4.31 min.

Triple-anchoring -EMR was successfully performed by an en bloc resection in 14/15 patients (93.3%) with free resection margins (R0) obtained in 13/15 patients (86.7%). The only unsuccessful T-EMR requiring a completion with classic EMR due to an incomplete en bloc resection was performed on a lesion with a poor lifting sign due to a central scar resulting from a previous polipectomy.

Table II. Kudo classification of the polyps resected

Kudo	Frequency	Percent (%)
IIIs	2	13.3
IIIL	6	40.0
IV	3	20.0
Vi	1	6.7
IIIs – IV	1	6.7
IIIL – IV	2	13.3

The mean number of clips placed after procedures was 5±1.77.

The main technical characteristics of the performed T-EMRs are summarized in Table III.

Table III. The main technical characteristics of the performed T-EMRs

	n	Mean	Std. deviation	Frequency	Percent (%)
Procedure time (min)	15	22.13	4.31		
No. of clips placed	15	5	1.77		
En bloc resection	15			14	93.3
Free resection margins (R0)	15			13	86.7

No major intra-/peri-procedural or delayed complications occurred. In 3/15 (20%) patients minor intraprocedural bleeding occurred; it was successfully endoscopically treated with injective therapy with adrenaline and/or clips placement.

Post-procedural histological analysis of the lesions showed that 13/15 lesions (86.7%) were adenomas, and their characteristics are summarized in Table IV.

Table IV. Histologic features of adenomas population

	Frequency	Percent (%)
Tubular adenoma with LGD and focal HGD. Free margins	2	15.4
Tubular adenoma with HGD. Free margins	1	7.7
Tubular adenoma with LGD. Free margins	4	30.8
Tubulo-villous adenoma with HGD. Free margins	1	7.7
Tubulovillous adenoma with LGD and focal HGD. Free margins	3	23.1
Tubulovillous adenoma with LGD. Free margins	1	7.7
Tubulovillous adenoma with LGD. Lateral margins with focal LGD. Free deep margin	1	7.7

One lesion, macroscopically considered as a LST-G mixed polyp characterized by a Kudo pit pattern IV, was a moderately differentiated (G2) early colorectal cancer, with no lymphatic or vascular angioinvasion, a 95/5 adenoma/adenocarcinoma ratio, no tumoral budding, positive resection margins (0.7 mm), depth of submucosal invasion <2 mm and width of submucosal invasion <4 mm (Ueno 2004), Kikuchi classification not assessable, TNM version VIII: pT1. Considering the patient's age, comorbidity and his will, together with the histological analisys, we decided to continue with endoscopic follow-up rather than addressing the patient to surgery.

Another lesion resulted in being diagnosed as an early colorectal cancer. It was characterized by a Kudo pit pattern VI and was endoscopically treated because it appeared as a sessile lesion (without ulceration or central depression below the mucosal surface) liable to an attempt with endoscopic resection. Its histological examination showed focal mucinous aspects, poorly differentiated grade (G3), no lymphatic or vascular angioinvasion, 95/5 adenoma/adenocarcinoma ratio, positive tumoral budding, free resection margins, depth of submucosal invasion of 2 mm and width of submucosal invasion of 4 mm (Ueno 2004), Kikuchi classification not assessable, TNM version VIII: pT1. Because a Lynch syndrome was diagnosed, the patient underwent a total colectomy.

A follow-up colonoscopy with biopsies on the post-polypectomy scar was performed 6 months after T-EMR in order to assess any potential macroscopic and histologic recurrence, which occurred in only one patient (6.7%), who was the same showing positive margins at the histological analysis of the resected lesion (Table V).

Table V. En bloc resection, free resection margins (R0), complications and macroscopic and histological recurrence at a 6-month colonoscopy

Event	No. Events	No. procedures	Percent (%)
En-bloc resection	14	15	93.33
R0	13	15	86.67
Intra-procedural complicances	3	15	20
Late complicances	0	15	0
Macroscopic and microscopic recurrence at 6 months	1	15	6.67

According to a linear correlation analysis, a positive correlation was found between procedure time and size of the lesions (r=0.678; p=0.005), between the procedure time and number of clips placed (r=0.851; p<0.001), and between size and number of clips placed (r=0.753; p=0.001). This may mean that T-EMRs in larger lesions can be more difficult, that a larger resection base needs more clips and that a greater number of clips placed requires more time.

There was no significant difference between the mean sizes of the right colon and left colon lesions (t=-1.023; df=13; p=0.325). There was no significant difference between the mean procedure times of right and left colon lesions (t=0.500; df=13; p=0.625).

DISCUSSION

Endoscopic mucosal resection has been widely used to treat colorectal polyps [15]. It is a safe procedure [16-18] that allows minimally invasive, organ-sparing endoscopic removal of benign and early malignant lesions of the gastrointestinal tract [18]. As most colorectal cancers develop from colorectal adenomatous polyps, EMR represents an effective preventive treatment for colorectal cancers [15]. However, it does not allow an en bloc resection of lesions ≥20 mm in size and in these cases piecemeal EMR is required [3]. Piecemeal EMR is related to local recurrence [3, 19] and to a poor histopathological evaluation [3]. Moreover, in case of superficial invasive carcinoma, to allow an adequate examination of the hystologic features, en bloc resection is necessary [8].

Therefore, if on one hand EMR remains a suitable option in neoplasms <20 mm in size [20], on the other hand, for larger lesions ESD has been developed to overcome limitations of piecemeal EMR, enabling the endoscopist to achieve en bloc resection regardless of tumor size [3, 8, 21, 22]. Endoscopic submucosal dissection is also related to a low rate of local recurrence compared with conventional EMR [15, 23, 24].

However, ESD is technically difficult, requiring considerable endoscopic skills and being related to a higher risk of adverse events [8]. Therefore, if ESD is now accepted as one of the standard treatments for large gastric tumors, on the other hand, it is not yet widely used for colorectal tumors [25]. Furthermore, the ESD technical problems can lead, other than to a high risk of adverse events, also to long procedure times.

Endoscopic submucosal dissection and EMR are not mutually exclusive and a hybrid technique may represent a good compromise between the technical demands of a complete ESD and the feasibility of EMR. In literature, different types of hybrids EMR/ESD have been reported [6, 25, 26]. They generally consist of a circumferential incision and partial submucosal dissection of the lesion followed by an en bloc snare resection.

Some data suggested that hybrid techniques might be less effective for en bloc resection of large colorectal lesions when performed as a rescue treatment, but they had a better outcome if used as scheduled treatment [6, 13, 25, 27, 28].

Moreover, there are some colorectal lesions that cannot be fully cured by piecemeal resection and lesions <30-40 mm that are often not suitable for ESD because of a difficult access into the submucosal layer. For the treatment of these lesions

the hybrid technique is expected to get better results than conventional EMR [6].

In our study we proposed a novel technique of hybrid EMR/ESD, the triple-anchoring EMR (T-EMR), for the treatment of colorectal lesions between 20 and 30 mm in size (lesions not suitable for en bloc EMR and not big enough to require an ESD). With this new technique we successfully performed an en bloc resection in 14/15 patients (93.3%) with R0 obtained in 13/15 patients (86.7%).

A similar technique was proposed recently by Pioche et al. [29] who proposed anchoring only the tip of the snare in a similar manner. However, although they achieved the en bloc resection in 92% of the lesions up to 20 mm in diameter, it was feasible in only 68.4% of the lesion 21-30 mm in dimaeter, with R0 achieved in 55.3%. Comparing Pioche's data with our study suggests that two more additional anchor sites, left and right to the lesion, can significantly improve the resective performance with a minimum extension of the procedure time.

Unlike the other hybrid techniques (requiring an endoknife in addition to the snare) [6, 25, 26], T-EMR is performed only by a snare for both incision and resection of the lesion. Moreover, the T-EMR tecnique requires only mucosal incisions (one at the top and two at the margins) and not a partial submucosal dissection. This method, without dissection (considered the most difficult aspect of colorectal ESD), is expected to reduce the procedure time and to decrease the rate of complications such as acute or delayed perforation. In our series no major complications occurred. The complications observed were minor bleeding during the procedure in 3/15 patients. Furthermore, relatively short mean procedure time made it possible to conduct all the procedures in conscious sedation only.

Other than the safety of the procedure itself, one of the possible reasons of the absence of delayed bleeding or perforations could be the ulcer closure by clip placement at the end of all procedures. It was previously reported that the prophylactic clipping of resection site after the endoscopic resection of large (≥20 mm) colorectal lesions reduced the risk of delayed post-polypectomy hemorrhage and did not increase the costs of hospitalization [30, 31]. However, the number of clips placed could correlate with an increased procedure time. Nevertheless, the mean procedure time in our study was lower or similar to that reported in the literature for other hybrid techniques [6, 15, 26]. More factors possible influencing low occurrence of complications in our study could be the partial and not circumferential mucosal incision as well as the absence of the submucosal dissection. The use of only one snare could make our technique accessible and cheap.

According to our data the T-EMR technique seems to be an effective and safe option to treat colorectal lesions between 20 and 30 mm in size. It ensures the reliability of an en bloc resection of large lesions with a lower procedure time. It may represent an alternative to ESD or a bridge to approach ESD for Western endoscopists who do not have enough cases of ESDs for training. Moreover, it may represent a good treatment when colorectal ESD cannot be performed. The major advantage of this technique is its easy application in the everyday practice because the snare technique is familiar to most endoscopists and because this procedure takes a shorter time without compromising the en bloc resection rate.

The main limitations of our study are the small population sample size, the few centers involved, the size of the selected polyps and our way of calculation of the procedure time (we considered also the time of clips placement that interfered with the real evaluation of the resection time based on the size and side of the lesion). Moreover, only skilled endoscopists were involved and this could have improved the complication rate.

Other studies enrolling more cases, more centers and more endoscopists (also basic or at least intermediate skilled), with a randomized comparison between ESD and T-EMR for resection of colorectal lesions are required to confirm the efficacy and safety of this procedure before its acceptance as a standard treatment. A larger number of patients could also better address the evaluation of the impact of the size and location of the lesions regarding the procedure time.

CONCLUSIONS

According to our preliminary case series, T-EMR seems to be a safe and effective procedure for resection of colorectal lesions between 20 and 30 mm in size.

Conflicts of interest: None to declare.

Authors' contribution: J.H., S.F.V.P and MB designed the study and conducted the procedures. S.S, A.P and F.B. collected the data. S.B. was responsible for pathohistological analyses. N.P and S.F.V.P. performed the statistical analyses and drafted the manuscript. S.M., M.B, and G.C. revised the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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